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NERVE ENDINGS IN MAMMALIAN MUSCLE.

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Since Ruffini [1898] gave us his beautiful drawings of muscle spindles, and Sherrington [1894] showed that they were sensory end-organs, our knowledge of their function and importance has been steadily growing owing to the observations of physiologists in many parts of the world, and particularly to those of Sherrington and his co-workers.

Until recent years our knowledge of the behaviour of the sense organs in muscle was obtained by inference and indirect observations. The only direct observations on mammalian proprioceptors made hitherto are those of Forbes, Campbell and Williams [1924], and McCouch, Forbes and Rice [1928], who, using a string galvanometer, were able to show that sensory action currents occurred after a muscle had contracted. But now the methods pioneered by Adrian have made direct observation of the response of these nerve endings possible, and it has only been necessary to adapt the technique to the peculiarities of the problem for the behaviour of mammalian muscle spindles to be studied directly.

A considerable amount of work has already been done on the nerve endings in frog's muscle [Adrian and Zotterman, 1926*a*; Bronk, 1929*a* and *b*; Matthews, 1929*b*, 1931*a* and *b*], but the histology of the nerve endings in mammalian muscle is far more complex than that of the muscle spindles in the frog, and does not justify the assumption that they behave in exactly the same way.

The present work has been undertaken to see what can be learnt of these nerve endings by direct observation, and this paper is a general survey of the subject, as the work has raised many new problems which have not as yet been fully examined.

The technique employed is essentially the same as that by which muscle spindles in the frog were studied [Matthews, 1931*a*, *b*], but many modifications in details have been necessary.

In any study of nerve endings by the electrical method it is almost essential to work with single nerve endings in order to discover the finer details of their behaviour and avoid statistical effects. It is much more difficult to isolate single nerve endings in mammalian muscles than in those of the frog, for the frog most conveniently possesses a small muscle containing only one spindle, and this has only a single sensory nerve ending. In mammalian muscles not only are there a number of spindles each containing several sensory nerve endings, but other endings are present as well, *e.g.* the tendon endings, small fibres which end among the blood vessels, and endings in the fascia associated with the muscle. It has not been found possible to confine the stimulus to single nerve endings, and so it has been necessary to restrict the fibres under observation. This has been done by the method, first used by Adrian and Bronk [1928], of cutting through the nerve below the recording electrodes until only one sensory fibre remains intact, and several hundred single nerve endings have been examined by this means.

Part I. Method.

Electrical recording apparatus.

The oscillograph and amplifier which have been described in previous papers [Matthews, 1928, 1929*a*] were used for the present work; the oscillograph was fitted with a reed of natural period 6500 vibrations per sec. and was critically damped electromagnetically by short-circuited copper loops on the extremities of the pole pieces. The distortion of nerve action potentials recorded at body temperatures will be appreciable, but these distortions do not enter into most of the results considered in this paper and so may be neglected; as it is the spacing and frequency of the action potentials which are the principal physiological interest, their time relations here are at present of lesser importance.

Small coupling condensers (0·001 μF) were used in the amplifier in the way previously described [Matthews, 1931*b*] in order to allow of recording sensory action potentials a few thousandths of a second after the whole nerve trunk had been stimulated electrically. In some experiments larger coupling condensers (0·25 μF) were used when the shape of the action potential was examined, and in a few very large condensers were used (4 μF) to see if there was any evidence of the presence of very slow action potentials which might fail to be recorded when the small condensers were in use. The output of the second stage of the amplifier was also fed to a three-valve amplifier feeding a loud speaker.

Camera.

The two-record camera giving simultaneous records at 5–20 cm. per sec. and at 2–4 m. per sec., which has already been described [Matthews,

1931*a*], was used to record the deflections of the oscillograph, the myograph and the time marker. In some experiments a Cambridge Instrument Co. 59 mm. paper camera was used when the width of cine bromide paper was insufficient to accommodate the whole record. Its driving gear was removed and it was driven by a powerful (Electromphone) electric gramophone motor, working direct on to the paper roller shaft through a universal joint; this gave the paper speeds from 5 to 20 cm. per sec. A rotating mirror device, such as has been previously described [Matthews, 1929*b*], was used to observe deflections before and during photographic recording.

Myograph.

A special type of myograph was designed and made for this investigation in order to record tension, extension, speed of loading, and contraction of the muscles. It is illustrated in Fig. 1.

The whole was built up on a small steel girder to which the drills in the animal's leg were clamped by insulated bushes so that the girder could be earthed for shielding purposes without earthing the body of the animal. A sliding carriage (*B*) carried the myographs which were of the torsion spring type and also a spring which could be used as an inertialess load for isotonic recording. The principle of this is illustrated in the inset to Fig. 1. A clock-spring barrel was used; the spring could be wound to any desired tension and when the muscle shortened the load only rose by 1–2 p.c. As the weight of the moving parts was only a few grams, inertia difficulties were eliminated. The whole myograph carriage was arranged to slide on a 7/16 silver steel rod (*C*) and a flat guide plate (*D*); it moved between adjustable stops, and a range of movement of up to 6 cm. was available. The rate of movement of the carriage was controlled by a dashpot (*E*) operating through a bell crank; a screw-down steam valve (*J*) regulated the flow of fluid from below to above the piston. The carriage was driven forward by a plunger in a cylinder (*G*) connected to the compressed air supply (25 lb. per sq. in.); it was returned by a smaller piston and cylinder (*F*). The carriage could thus be moved forward, stopped and returned in any way required by manipulation of the air-supply, stops, and dashpot valve.

Light was directed on to the myograph mirrors from the same arc light that illuminated the oscillograph; it was arranged that the incident and reflected beams were exactly in the line of travel of the carriage, so that there was no shift of zero as the carriage travelled forward. The distance from the mirror to the camera was about 7 m., so that there was no appreciable change in magnification when the carriage travelled a centimetre, which was about the movement usually employed. The carriage was designed so that all the strains came under the centre line of the rod on which it slid, so that there was no tendency for it to slew to either side; had any unsteadiness occurred it would have been very apparent, as it would have been enormously magnified by the 7 m. beam of light; absolutely no trace of such unsteadiness could be detected as the carriage moved, which may be attributed to the central disposition of the strains and the very excellent fit of the carriage on its slides. The coarse vibrations in some of the tension records below are due to the vibration of the bench on which the myograph was mounted. The tension myograph carried two mirrors, one near the end and a second giving five times as much magnification near its centre; this was found a great convenience, as small tensions applied to a muscle could be read with

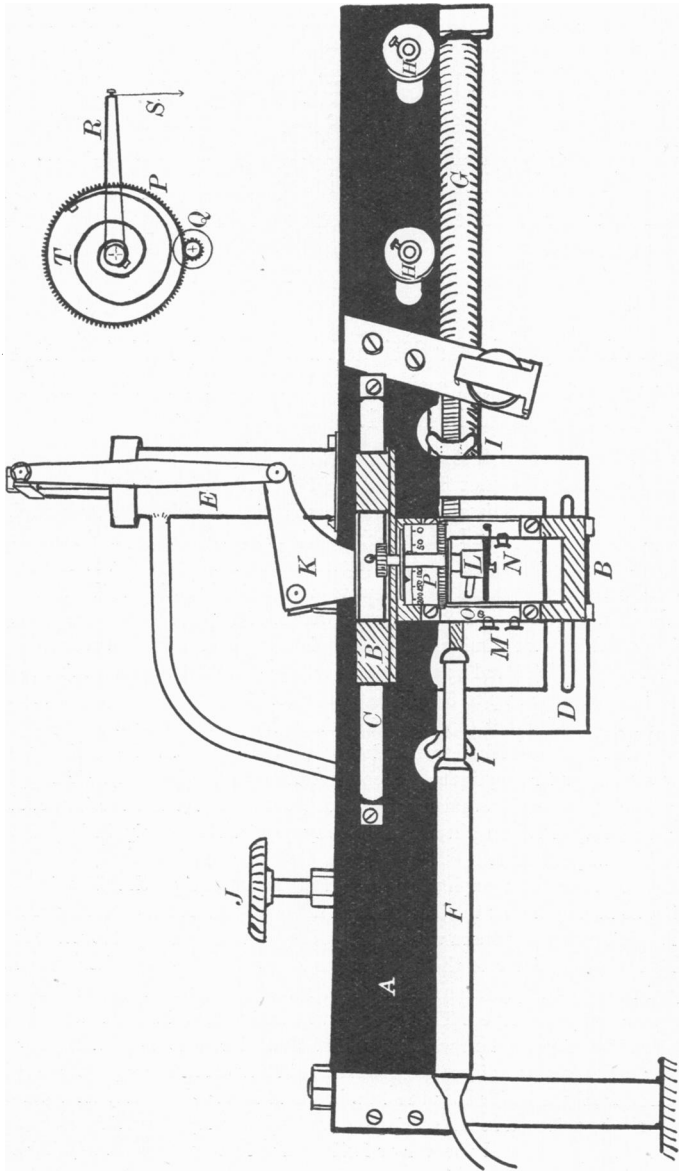

Fig. 1. Sketch plan of myograph. Inset, diagram of isotonic load device. *A*, steel girder; *B*, moving carriage; *C*, slide rod; *D*, guide plate; *E*, dashpot; *F*, return cylinder; *G*, forward drive cylinder; *HH*, bushes to take drills in bones; *II*, adjustable stops; *J*, screw-down valve; *K*, bell crank; *L*, boss on spring shaft; *M*, isometric myograph mirrors; *N*, isotonic and extension mirror; *O*, isometric myograph spring; *P*, spring barrel; *Q*, spring winder; *R*, isotonic myograph lever; *S*, wire to tendon hook; *T*, spring.

accuracy from the sensitive mirror while the less sensitive one could record large tensions (*e.g.* during tetanic contraction) after the other beam had deflected right off the camera slit. A third mirror recorded the movement of the arm of the isotonic spring load; if a thread was attached to this arm and to a pin on the main girder this mirror could be used to record movement of the carriage and thus extension of the muscle.

With this myograph the muscle can be stretched or released by any amount at any desired rate or loaded or unloaded at any rate. Moreover, every mechanical change in the muscle is recorded on the film, with the coincident electrical record.

Stimulating arrangements.

For electrical stimulation of the nerve two methods were used, a coreless induction coil with close coupled coils and a calibrated rheostat in the primary circuit, and a neon lamp apparatus. The latter was found extremely convenient, as the rate of stimulation could be varied instantly by altering the capacity across the lamp and the charging resistance, and the strength varied by a potentiometer in series with the lamp. Either stimulating circuit could be connected to the Ag-AgCl type stimulating electrodes through 0·001 farad condensers to prevent any steady current leakage and to abbreviate the stimulus escape.

Material.

Cats were used in all the experiments described here. Guinea-pigs were used in a few preliminary experiments, but were not found to be very suitable owing to their small size and frailty.

In most experiments the animals were anæsthetized with chloroform and ether and decerebrated, at first with a Sherrington frame, in later experiments by trephining; the sciatic and femoral nerves and the attachment of psoas were cut under anæsthetic to immobilize the limbs. In some early experiments urethane (1 g. per kg.) was used, but it was discontinued as it was found to affect the response of the nerve endings; this will be discussed in detail later. Spinal animals were not found to be very satisfactory owing to the low blood-pressure and difficulty of correct ventilation; any deviation from normal in these respects was found to alter the response of the nerve endings.

Shielding, etc.

The animal was placed on a wooden stand in a large earthed iron box to which the myograph was bolted. The box had a detachable plate-glass front and served both for shielding the preparation from electric and magnetic disturbances and also for warming; the floor was heated with a gas ring and was flooded with water to keep the air moist. In some experiments the nerve was enclosed in a moist chamber, obviating the

necessity of flooding the box. The trachea tube was arranged so that the animal could either breathe cold air from outside the box or warm air from within. Temperatures were observed with a needle thermocouple connected to a galvanometer recalibrated in ° C.; the cold junction was housed in a thermos flask. Thus the body temperature of the cat could be observed, or that of the muscle under observation only, by inserting the needle under the skin close to the muscle. An electrically heated pad was sometimes used to raise the temperature of a limb; it was supplied from an accumulator, one pole of which was earthed to avoid bringing electrical disturbances into the animal box. Steel hooks were tied into the tendons and connected to the myograph with steel wire.

Isolation of single nerve endings.

Various methods of isolating the response of single nerve endings were tried. It seems unlikely that muscles exist in the cat which contain only one sensory ending such as were found in the frog's toes [Matthews, 1931*a*], though muscles have been described containing two or three muscle spindles [Hines and Towers, 1928]. It was therefore necessary to take a muscle containing a number of nerve endings and put all but one out of action. Preliminary experiments in which the muscle was divided showed that it was possible to isolate single endings in this way (which was used by Adrian and Zotterman [1926*a*] in their first isolation of a single nerve ending in frog's muscle), but in cats the endings obtained in this way rapidly deteriorated and soon failed altogether. Perhaps their failure was in part due to liberation of harmful substances in the muscles, but the chief factor was probably the almost inevitable failure of their blood supply resulting from cutting the muscle, for later experiments have shown that the behaviour of nerve endings in muscle is modified by circulatory arrest, and the endings fail a short time after the blood supply of a muscle is cut off. This method was therefore abandoned.

Another method which was tried was that of blocking conduction in the nerve below the recording electrodes by means of a constant current passing between a second pair of electrodes, for I have found in experiments on the frog (unpublished) that by minutely controlling the blocking current conduction can be suppressed in all but one sensory fibre, so that the response of a single ending can thus be followed in a preparation containing a number of nerve endings. However, when this was tried on cat's nerve it was found that the steady blocking current provoked a random discharge of impulses in the nerve and often started rapid discharges of the type described by Adrian [1930] and shown by him to originate in

damaged fibres or endings. Also it is impossible to be sure that the one sensory fibre which is not blocked is conducting normally and transmitting all the impulses which come to the polarized region. This method was therefore also abandoned in favour of section of the nerve between the muscle and recording electrodes. This method, which was used by Adrian and Bronk [1928] to isolate the response from a single motor nerve cell, and by Bronk [1929*a*] to isolate endings in frog's muscle, does not suffer from any of the disadvantages of the methods discussed above. It only presents difficulty in the dissection of the nerve, but after some practice it is possible to make a successful single nerve ending preparation at nearly every attempt, and more than two hundred have been made in the course of the present work.

The dissection of the nerve is carried out on a black glass plate under strong light with a low-power dissecting binocular, using needles sharpened to a cutting edge on an oil-stone; the nerve sheath is removed for a short distance and the nerve separated into bundles of fibres; these are cut in turn and after each section the upper part of the nerve is placed on electrodes and the appropriate muscle is stretched. From the sound of the amplified action currents in the loud speaker it is possible to tell by ear how the dissection is proceeding. When only the last bundle remains unsevered the response has as a rule resolved itself into a countable number of superimposed rhythmic discharges, and redivision and section of the remaining bundle is carried on until only a single rhythmic response results on stretching the muscle. If a slip is made and all response is abolished the section can be repeated lower down if a long stretch of nerve is available.

The nerve-section method of isolating nerve endings selects one of the endings present entirely at random; if a number of different types of ending are present one type is selected by chance in each experiment. Moreover, if a large number of preparations are made the endings selected by section should indicate all the types present, and the relative frequency with which each type is met with will roughly indicate the proportion in which the various types of ending occur in the muscle. Actually four types of behaviour have been met with in single-ending preparations.

When the nerve is divided into its natural components it is necessary to remove as much as possible of the connective tissue from the nerve bundles, for if this be left on the nerve in a damaged state discharges of the type described by Adrian [1930] coming from endings associated with the nerve sheath and blood vessels occur and somewhat mask the impulses from the endings in the muscle. Fortunately they can be distinguished from the latter, as they are quite unconnected with stretching of the muscle, and to avoid them most of the nerve sheath is stripped off.

The responses in the nerves of a number of muscles have been examined (sartorius, gastrocnemius, tibialis anticus, peroneus longus, peroneus brevis, soleus, and various toe muscles). The most detailed study has so far been carried out on peroneus longus and soleus, and sufficient results are to hand to form some idea of the behaviour and relative abundance of the different types of nerve ending in these two muscles. The results from other muscles do not show any obvious difference from these two muscles.

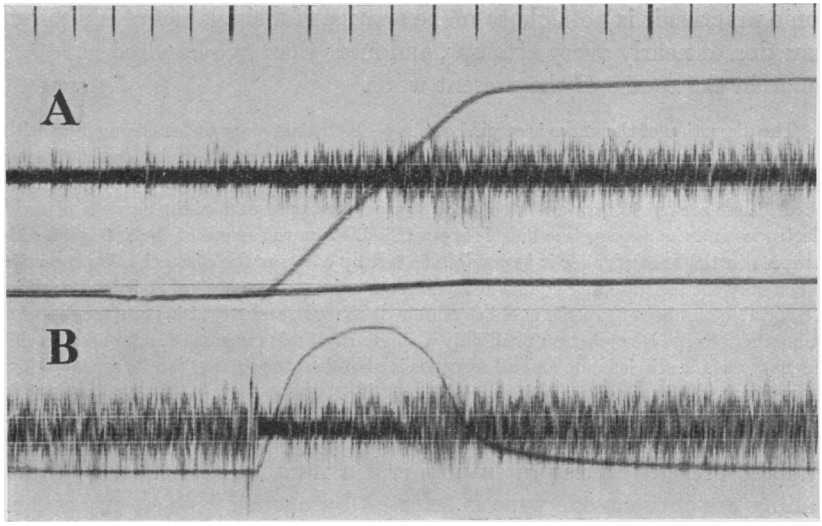

Fig. 2. Response from whole nerve to soleus. A, on stretching, cross-line signals extension, bottom line tension (final value about 10 g.). Centre oscillogram. B, during isotonic twitch, tension 50 g. Time marker at top 0·05 sec. intervals. This and all subsequent figures read left to right and are about half the size of the original records.

Results.

If a muscular division of either the peroneal or popliteal nerve be placed on the electrodes while the muscle attachments are intact, there is an irregular discharge of impulses continually in progress. This discharge originates in the muscle proprioceptors, for it is greatly reduced if the tendon of the appropriate muscle be freed from its attachments. The slight residual response when the muscle is quite free ceases for a few seconds if the muscle be stretched and released, and then gradually recommences. It thus appears that a number of the endings in muscle set up a resting discharge in the absence of stimulation, but later it will be

shown that they do not all do so. If the muscle be stretched there is an enormous sensory response and the action potentials from so many fibres are superimposed that analysis is impossible.

When the muscle is stretched and kept under tension, even of only a few grams, a large irregular discharge of impulses occurs in its nerve, and this continues indefinitely as long as the tension is maintained. This is illustrated in Fig. 2 A, which shows the response from soleus, and Fig. 2 B shows the response when the muscle contracts in response to a maximal stimulus applied to the nerve below the recording electrodes (by a second pair of electrodes). It is at once clear from the complexity of the response that the details of the behaviour of these end-organs can only be learnt by studying them singly.

It has been mentioned above that four types of behaviour have been met with in single-ending preparations. The four types of behaviour have been designated A 1, A 2, B and C for convenience in reference and will be described successively. The distinction of these types of behaviour is based not only on the response of the preparations to passive stretch but also on what happens to the response during active contraction of the muscle; as will be seen the different types of behaviour are totally distinct and readily identified.

Part II. The types of receptor present.

A 1 *type of behaviour.*

This type of response is that most frequently met with and has been found in every muscle that has been examined; about 50 p.c. of all the endings isolated have been of this type. The behaviour of these receptors is very like that of the frog's muscle spindles.

Response to stretch.

The endings giving the A 1 response have a very low threshold, and the least tension on the tendon, even 1 or 2 g., is sufficient to evoke a rhythmic discharge of impulses from them; in addition, in a number of preparations a regular discharge (5–15 per sec.) is present in the absence of external tension, but this ceases entirely for a few seconds after the muscle has been stretched and released, and then gradually builds up to its old rate again. But in about two-thirds of the preparations this resting discharge is absent. When present, in many preparations one or two impulses are set up at each heart beat, and these vanish instantly when the arteries are clamped, but more often the resting discharge rate does not

correlate with the heart beat. The receptors in mammalian muscle differ very markedly from those in the frog, in that they are able to set up discharges which are regular at very low frequencies. In the frog at 15° C. regular discharges below 15 per sec. rarely occur, discharges below this frequency being a random succession of impulses. These mammalian endings, however, often set up regular discharges at rates as low as 5 per sec., and the spacing of the impulses does not differ from the mean by 10 p.c.; irregular discharges above 10 per sec. have rarely been found. After

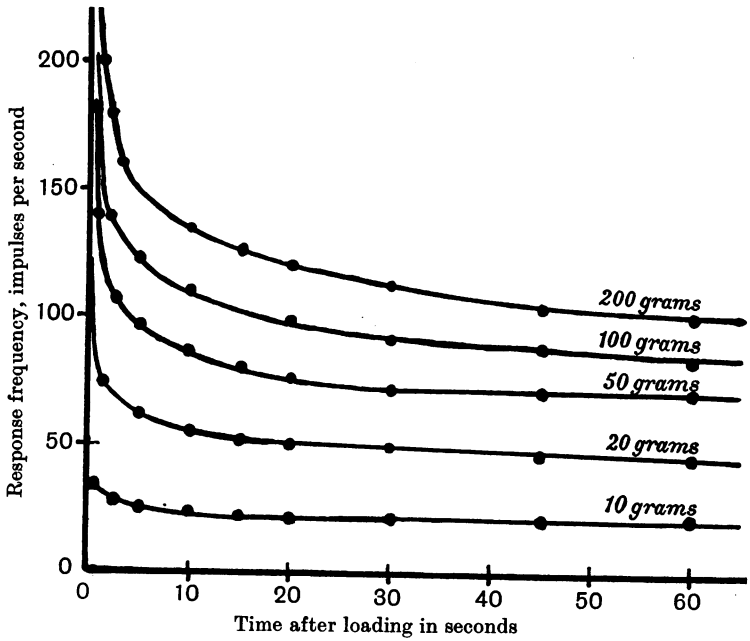

Fig. 3. Graphs of response to various tensions.

one of these endings has been subjected to a fairly big (250 g.) stretch for some minutes, its threshold on unloading is found to have risen considerably, for if thereafter it be restretched very gradually a higher tension is reached before it starts to respond than is the case when it is stretched without such previous loading; however, when the response starts it has about the same rate as the starting rate in the first case. The response frequency at any tension is slightly lowered if that tension immediately follows a previous stretch; this effect is most evident at low tensions. The effects of previous stretch on the response to subsequent restretch have not been worked out quantitatively on the endings in mammalian muscle,

but this has been done with the endings in frog's muscle [Matthews, 1931*a*], and the present observations suggest that here also the end-organ takes some seconds to return to its resting condition after it has been responding.

In Fig. 3 the response of one of these endings when various loads are hung on the tendon is shown graphically. Over this range the frequencies

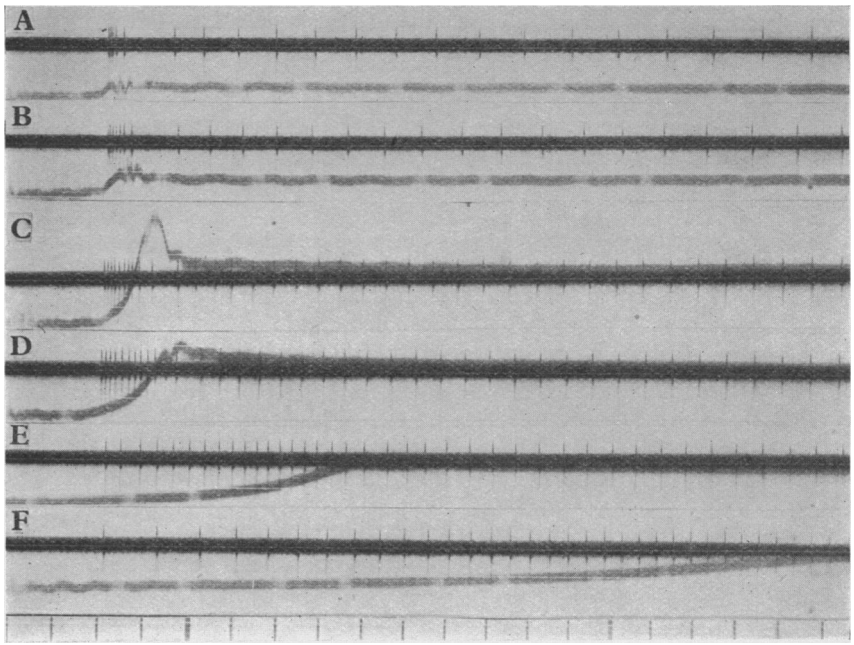

Fig. 4. Records of response from a single nerve ending (A 1), in peroneus longus. Electrical record and record of tension. A, B, C, stretch at 20 mm. per sec. to final tensions of 10, 15, 25 g. C, D, E, F, stretch at various rates to a final tension of 25 g. Time marker at bottom 1/20 sec.

set up are approximately proportional to the logarithm of the load on the tendon, as was found to be the case with frog's muscle spindles; at high tensions the response falls short of this proportionality. If the logarithm of load-frequency relationship be plotted the slope of the lines from different preparations is by no means the same. The graphs in Fig. 3 only cover the first minute after loading, but the end-organ continues to respond at a rate which declines more and more gradually, until after about an hour it becomes steady, and there seems no reason to suppose it would not continue thus indefinitely. In a few preparations the response has continued

to fall and ceased after a few minutes' loading, but the majority have continued to respond in the way described above. One preparation of a receptor in one of the interossei muscles of the cat's foot ceased to respond about 30 sec. after loading. With large loads of 500 g. and up-

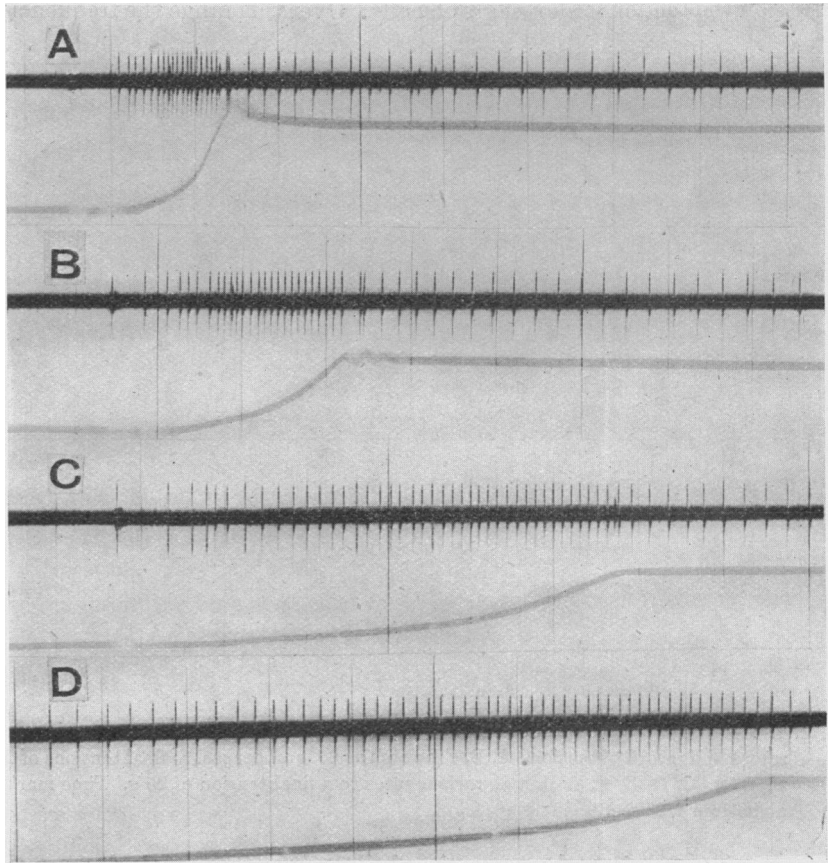

Fig. 5. Records of response of a single nerve ending (A 1) in soleus. Stretch to a final tension of 55 g. at rates indicated by the tension record. Cross-lines 1/10 sec.

wards the response may cease abruptly or undergo a transient acceleration a minute or two after loading, but it is thought that this may be due to the effects of constriction of the circulation rather than to adaptation (discussion of this phenomenon will be deferred to a later section of this paper, where the effects of circulatory arrest are considered).

Extension.

So far the response of the end-organ to steady tension only has been considered. It is found that during extension the end-organ responds at a high rate. In Fig. 4 C, D, E, F are shown records of the response when peroneus longus is extended by a fixed amount at various rates; Fig. 5 shows similar records from an ending in soleus, and in Fig. 6 these records are presented graphically.

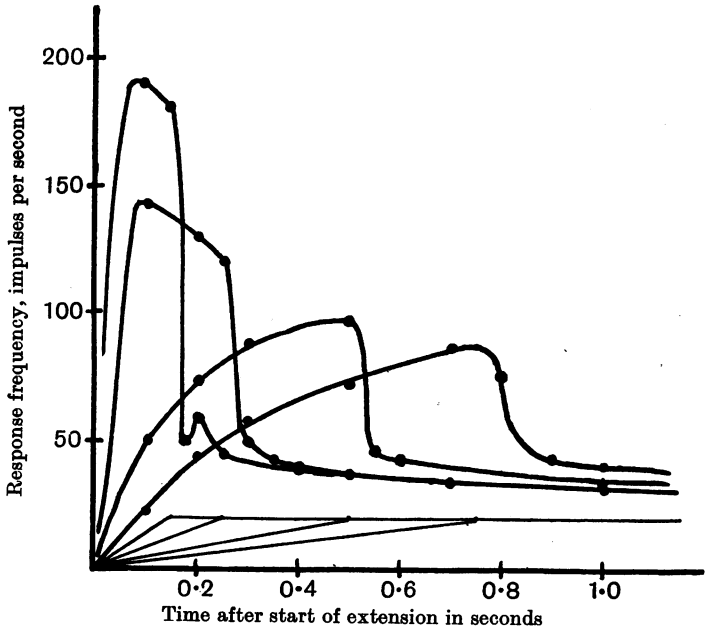

Fig. 6. Graphs of the response of an ending (A 1) in soleus. Stretched at rates indicated at the foot, to a final tension of 65 g.

If the stretch is very rapid the maximum frequency occurs during the stretch before the maximum tension has been reached (see Figs. 4 C, 5 A); the reason for this may be that with the very high frequencies that are set up adaptation is so rapid that by the time the maximum tension is reached considerable adaptation has already occurred. But several other possible explanations must be considered. It is found that the maximum frequency set up depends much more on the rapidity of stretching than on the final value of the tension; a slight stretch applied rapidly can evoke a very high initial frequency of response (see Fig. 4 A, B). This suggests

that during rapid stretch the stimulus to the nerve ending may rise far above its later steady value; this may occur on account of the mechanical properties of the end-organ.

Discussion of viscous effects.

In a previous paper in which similar effects were recorded from frog's muscle spindles it was suggested that the high initial frequency and rapid fall of frequency that occurred on rapid stretch might be due to the

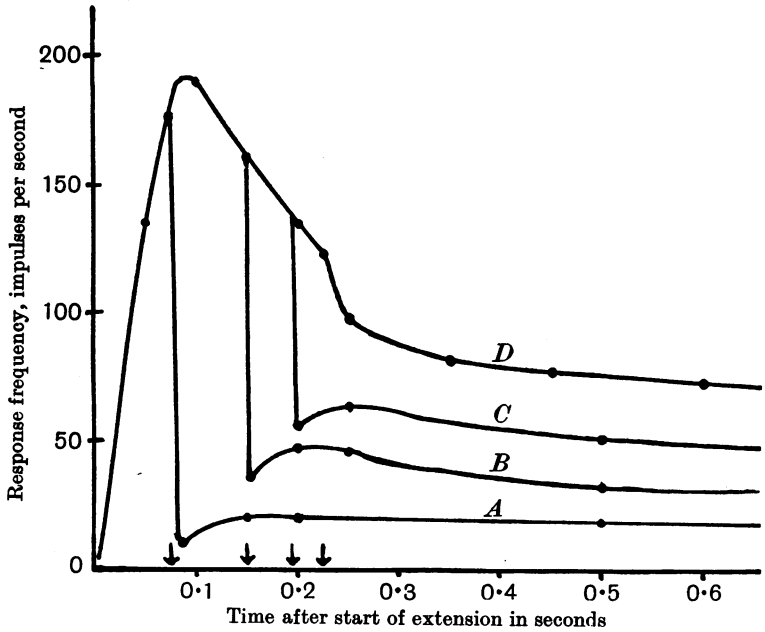

Fig. 7. Graphs of an A 1 ending in soleus stretched at a fixed rate to final tensions of 20, 50 100, 200 g. The arrows indicate the conclusion of extension in these four cases.

terminal portions of the structure on which the nerve ending was situated being more viscous than the centre; or alternatively, that the whole end-organ structure might be more viscous than the surrounding muscle fibres, so that during rapid stretch the deformation of the nerve ending would be much greater than after a steady extension had been reached. Whatever the arrangements may be the forces acting on a viscous elastic end-organ will be greater during extension than after equilibrium is reached in a new position. It will be seen below that the viscous elastic interpretation accounts very well for the observed behaviour of the cat's receptors, and support of the view that the end-organ is more viscous than

the surrounding muscle fibres comes from observations to be described later of the behaviour of the endings during active shortening of the muscle.

In Fig. 7 are shown graphs of the response when the muscle is extended by various amounts at a fixed rapid rate. When extension ceases (Fig. 7 A, B, C) the response does not fall smoothly to a lower level, but it abruptly falls below it and then rises up to it. This strongly supports the view that during stretch overloading of the end-organ is occurring owing

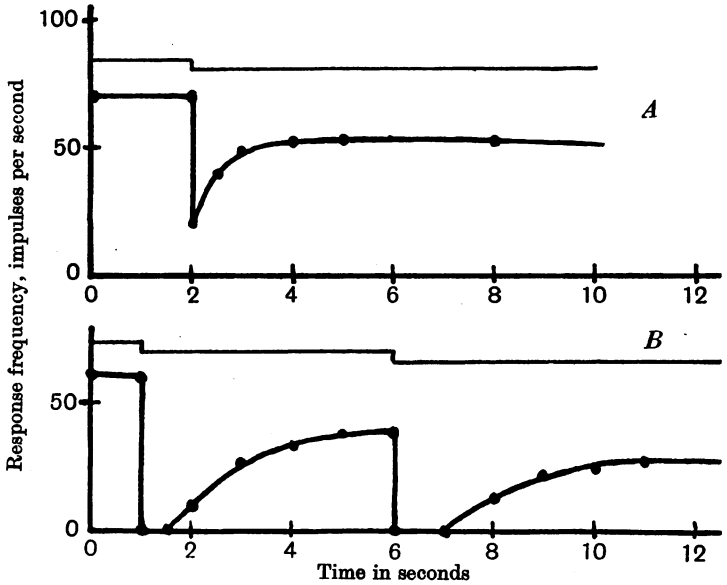

Fig. 8. Graphs of response on quick release. A, type B endings in soleus (to be discussed later in text). Tension 350 g. falls to 215 on release of 1 mm. B, type A 1 ending in soleus. Tension 160 g. falls to 95 and 60 g. on two successive releases of 1 mm.

to viscous forces. During stretch the stimulus to the end-organ would reach a value determined by the relative viscous elastic properties of the end-organ and surrounding muscle fibres; when extension ceases the strains on the end-organ will fall to those determined by the elasticity of the tissues. Thus at the cessation of extension the stimulus to the end-organ will fall to a lower value, causing a fall in the response which will then rise again as the adaptation caused by the previous greater stimulus and response passes off.

Quick release.

If a steady tension on the muscle be suddenly reduced to a steady lower tension the response stops and slowly rises up to the new lower

frequency. This is shown in Fig. 8 B from an ending in soleus. This again indicates that the end-organ may behave as a viscous elastic structure. The rise to the new frequency occurs much more slowly than the return of tension in the whole muscle, and though part of this rise may be due to adaptation produced by the previous greater stretch passing off gradually, it certainly accords with the view that the end-organ is more viscous than the surrounding muscle fibres. The rise noted above, and ascribed to disappearance of adaptation in Fig. 7 A, B, C, occurs much more rapidly than the rise after quick release.

In Fig. 7 D it will be seen that 0·1 sec. after the beginning of extension the response rate begins to fall although the tension is rising and extension still occurring; this fall in rate is probably partly due to adaptation on the part of the nerve ending.

Theoretical view of viscous effects.

The fall is response which occurs at the end of extension is much more marked when the final tension reached is small (Fig. 7 A) than when it is considerable; if viscous overloading occurs during stretch this is to be anticipated for the following reasons. The overloading stress in the end-organ due to its viscosity may be defined as the amount by which the force necessary to extend the end-organ by a small amount at a given rate exceeds that necessary to extend it the same amount infinitely slowly. Thus during extension the stress in the end-organ will be (a), the tension due to its elasticity, + (b), the overloading stress due to viscosity, which will depend on the rate at which it is being extended. When the rate of stretch is fixed b is constant, while a increases with the extension (though not in direct proportion). Thus as the extension increases the viscous overloading stresses become a smaller and smaller fraction of the total stresses in the end-organ; as a result the disappearance of (b) at the end of extension should have less and less effect on the response as the extension increases. Secondly, as the response rate varies as the logarithm of the steady tension on the muscle and therefore presumably roughly as the logarithm of the tension on the end-organ, large percentage changes in this tension will have far more effect on the rate of response at low than at high tensions.

From the above arguments it is clear that the initial overloading effect due to the viscosity of the end-organ should be most in evidence when the tension is small and the extension rapid, which is indeed the case (see Fig. 4 A).

Comparative rate of stretch.

If the records from soleus and peroneus longus be compared (Figs. 4 and 5) an interesting difference may be seen in the actual speed of stretch necessary to bring the rapid initial response into prominence in these two muscles. In Figs. 4 E and 5 B the rate of stretch is about the same, yet the ending in soleus responds twice as fast during stretch as it does later at constant length, while that in peroneus longus responds hardly any faster during stretch than subsequently. To obtain the same relative acceleration of response during stretch a much more rapid stretch must be given to peroneus longus than to soleus; the end-organs in soleus thus appear to be much more viscous than those in peroneus longus. It seems likely that the differences in viscous elastic properties of red and white muscle exist also in the intrafusal fibres of their muscle spindles, for evidence will be presented later which suggests that the A 1 type of response comes from nerve endings in the muscle spindle.

Other possible explanations of these phenomena.

The records obtained by Hartline [1932] of the impulses set up by single receptors in the eye of *Limulus* when suddenly illuminated look very like those obtained here by sudden slight extension of a muscle. As in Hartline's preparation there are no mechanical factors involved, it does not seem impossible that the abrupt fall in response to a sudden stimulus might be partly due to some fundamental property of nerve endings, such that they are able to respond at a high rate initially to a sudden stimulus but shortly fall suddenly to a much lower level of activity, although the stimulus is still present at full intensity. The possibility of something of this sort occurring cannot be entirely neglected, but it is very unlikely that the phenomena studied here are due to such properties of the nerve ending, as they seem to be very closely connected with the mechanical events in the muscle and end-organ and they do not occur with the B endings described below; though by the present methods it is impossible to dissociate completely the effects on the response of adaptation and yielding of viscous elastic structures, it is probable that both factors are of importance, each predominating under particular conditions. The peculiar features of the response of these endings seem to be due mainly to mechanical factors.

The records of Fig. 4 A and B bear a superficial resemblance to those obtained by Tsai [1932] when he recorded the response from a suddenly stimulated receptor (frog's muscle spindle) above a region of impaired conduction; the pause in the response here cannot be due to impulses being blocked somewhere on their way to the recording electrodes, for this pause can be abolished by altering the stretch applied to the muscle.

Maximum rate of response.

The highest frequency of impulses that has been recorded from these endings is about 500 per sec. The absolute refractory period of the fibres supplying these nerve endings would allow of somewhat higher frequencies being transmitted, for these frequencies can still be recorded when the temperature of the nerve is lowered to about 34° C., though if it

is lowered below this partial blocking of the response occurs. It follows that normally the limit is set by the nerve ending rather than the nerve fibre, as Adrian has shown to be the case for a number of types of receptor. However, such frequencies can only be evoked by extremely violent stretch (5 mm. in 1/50 sec.); it does not seem likely that such sudden stretch could ever occur in the intact animal.

Response during active contraction.

The A 1 type endings do not respond during active contraction of the muscle, and in this their behaviour closely resembles that of the frog's muscle spindle.

If the muscle is not subjected to any initial tension there is no response during contraction (see Fig. 9 F). If the muscle is subjected to initial stretch the response already in progress ceases during the rising phase of the mechanical response and restarts as the muscle relaxes. The behaviour of the A 1 endings is illustrated in Fig. 9, which shows the cessation of the response during isometric twitch A and B in peroneus longus, C and D in soleus, at low and high initial tension. In Fig. 9 C and D two impulses appear during the twitch; this has been seen in a few preparations, but usually the pause in the response is absolute. If shortening is allowed to occur the pause in the response takes place in the same way (see Fig. 9 E).

During isometric tetanic contraction the response ceases and restarts on relaxation at a slightly higher rate; this is illustrated in Pl. I, Fig. 10, A is recorded from an ending in peroneus longus and C from one in soleus. If the initial tension is considerable the response may not cease entirely during isometric tetanic contraction, but its rate falls considerably (see Pl. I, Fig. 10 D). When the muscle is tetanized for some seconds the response often gradually reappears at a greatly reduced rate. The response stops completely during tetanus if shortening be allowed (Pl. I, Fig. 10 B), and when the muscle relaxes after isotonic tetanic contraction a burst of impulses is set up as relaxation occurs which is very like that recorded when the muscle is suddenly stretched (cf. Fig. 4 B).

Strength of stimulus.

In all the cases considered above the stimulus was at least 30 p.c. supramaximal. If the stimulus be gradually reduced the pause during twitch becomes less marked as the mechanical response becomes smaller, and disappears with the twitch. If the stimulus be reduced during tetanus the response reappears as the tension falls, and when the stimulus becomes sub-threshold the response returns to that determined by the

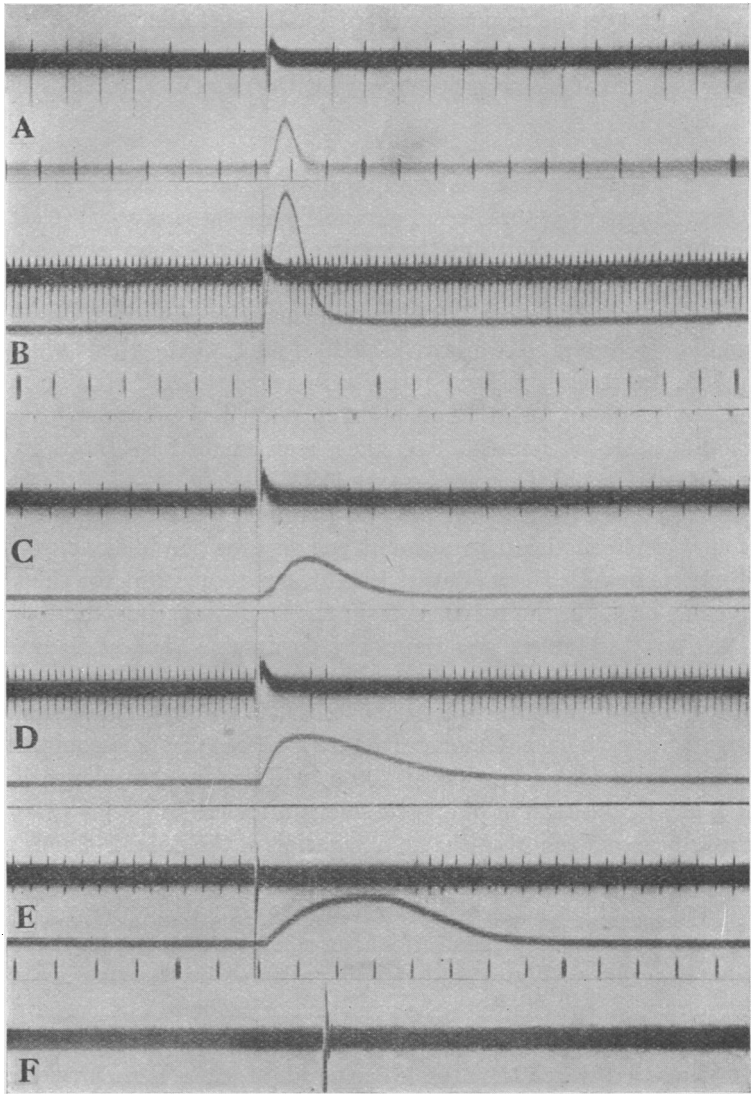

Fig. 9. Response of A 1 endings during twitch. A, B, peroneus longus. Maximal isometric twitch, initial tensions 10 and 200 g. C, D, soleus maximal isometric twitch, initial tensions 10 and 120 g. E, soleus, maximal isotonic twitch, tension 40 g. F, soleus maximal twitch tendon free. Time marker 1/20 sec.

stretch background. The rate of tetanization is not found to have any significant effect on the response except in so far as it affects the mechanical response. The rate is usually kept as low as will give nearly complete fusion, as higher rates confuse the record with frequent stimulus escapes.

Interpretation.

All the above observations seem to allow of only one interpretation, that these stretch receptors lie "in parallel" with the contractile elements which when they contract take the strain off the end-organ, and cause its response to cease. That this occurred in muscle receptors was suggested by Fulton and Pi-Suner [1928] to account for the silent period in mammalian reflexes. Hoffman [1919] found that when a muscle exhibiting the stretch reflex contracts in response to reflex or motor stimulation there is a cessation of action currents in the muscle during the contraction; this phenomena has since been studied in detail by the above authors and by Denny Brown [1928].

The view that the receptor lies "in parallel" with the muscle fibres was found when modified to account entirely for the behaviour of the frog's muscle spindle [Matthews, 1931*b*], but to account for the pause observed to occur in the response from the frog's muscle spindle during isometric contraction, it was necessary to assume that some internal shortening took place, which it was suggested occurred owing to the elastic yielding of the muscle extremities. This elastic yield assumed to be present has now been demonstrated by Eccles (personal communication), who finds that a tension of 200 g. will produce an elongation of about 1 p.c. in the tendon of a cat's soleus muscles.

Thus during twitch in soleus an elongation of the order 1–2 mm. is to be expected in its tendon. In Fig. 8 B is shown a graph of the fall in the response that occurs when a stretched muscle is suddenly released 1 mm.; the response stops, and only after some seconds begins to rise up to a new lower level. Thus the shortening allowed by the yielding of the tendon may well contribute to the cessation or reduction of the response which occurs during isometric contraction. If the initial tension is greater than that which the muscle can produce, there is no pause in the response when the muscle twitches and only a slight reduction in its frequency; under these conditions the action current and chemical changes are still taking place in the muscle, so these cannot be held responsible for the pause, which seems only to be associated with the mechanical changes in the muscle. If the A 1 type receptors lie in the muscle spindles their behaviour is entirely accounted for by the

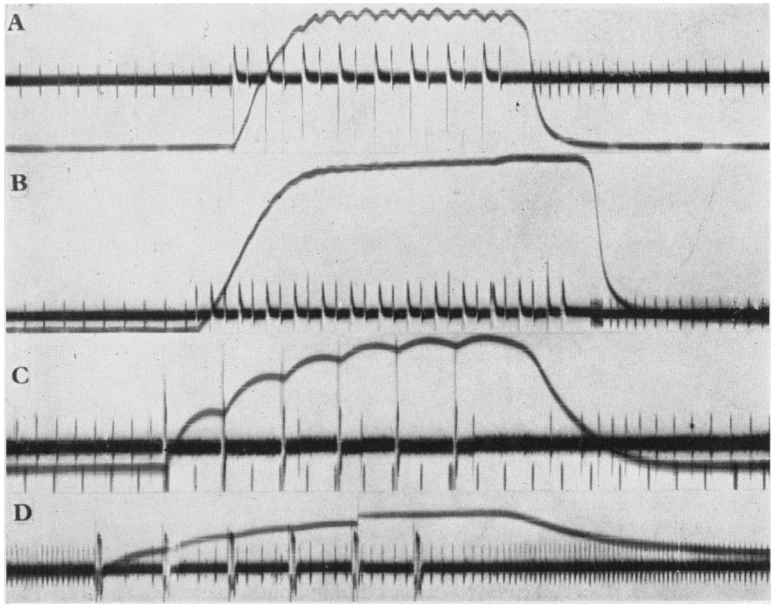

Fig. 10. Response of A 1 endings during tetanic contraction. A, peroneus longus. Maximal isometric tetanus. Initial tension 20 g. B, peroneus longus. Maximal isotonic tetanus. Tension 25 g. C, D, soleus maximal isometric tetanus, initial tensions 10 and 500 g. Time marker 1/20 sec. at foot of C.

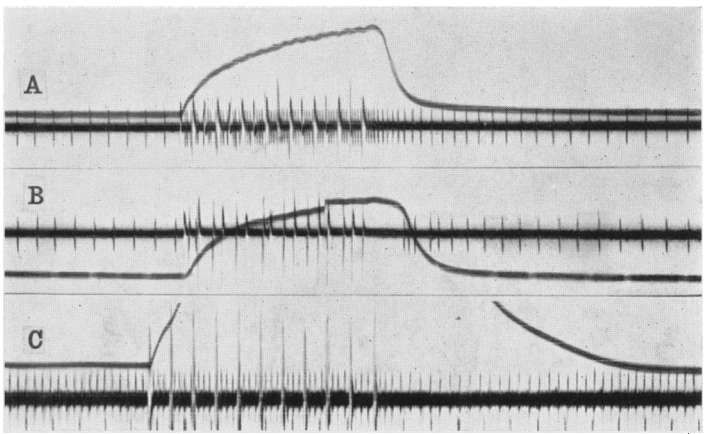

Fig. 11. Response of A 2 endings. A, B, peroneus longus, both from the same ending, initial tension 25 g. Stimulation in A maximal, in B 85 p.c. of maximal. C, soleus stimulation 110 p.c. maximal, initial tension 500 g. Time marker 1/20 sec. at bottom.

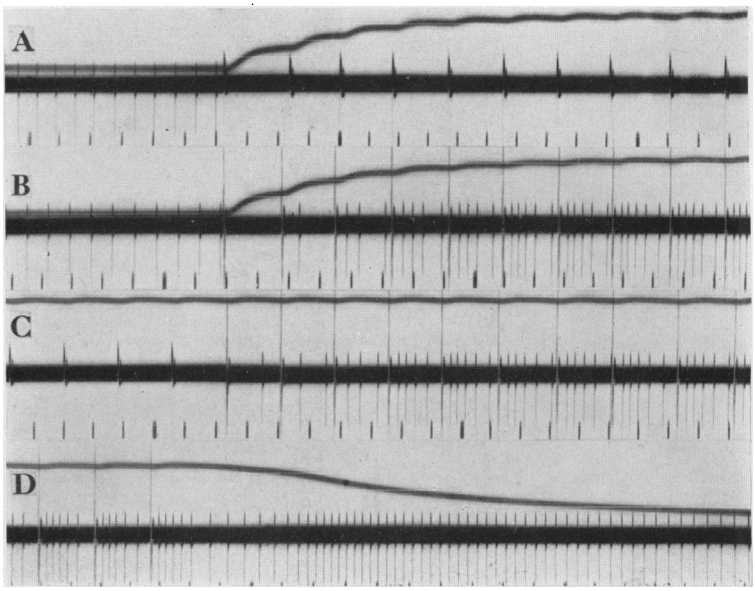

Fig. 12. Response of an A 2 ending in soleus during isometric contraction, initial tension 100 g. A, start of maximal tetanic stimulation. B, start of 110 p.c. maximal stimulation. C, tetanic stimulation; after the fourth stimulus escape the stimulus is suddenly increased from maximal to 110 p.c. maximal. D, conclusion of 110 p.c. maximal stimulation. Time marker 1/20 sec.

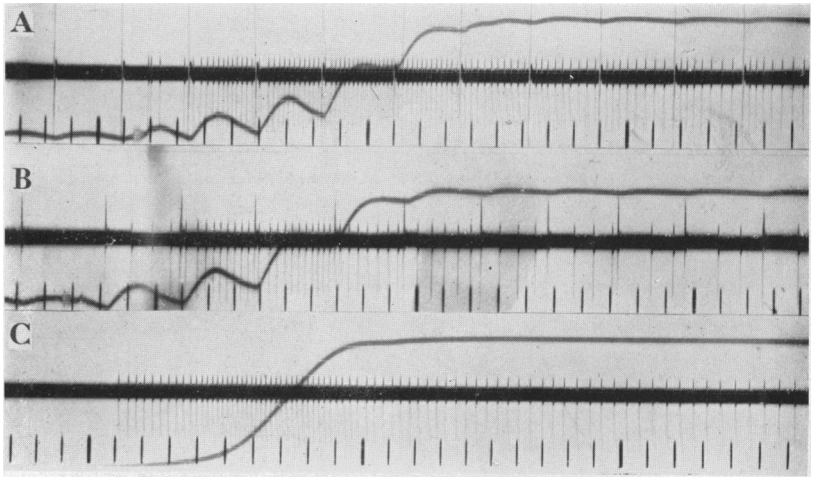

Fig. 13. Response from an A 2 ending in soleus. A, 110 p.c. stimulation muscle extended to approximately 300 g. tension. B, maximal stimulation, extension to 300 g. C, no stimulation extension to 300 g. approximately. Time marker 1/20 sec.

anatomical position of these receptors "in parallel" with the muscle fibres.

It has not yet been possible to identify the endings giving the A 1 response histologically as was done in the frog owing to the great number of nerve endings in the histological preparations that have been made. The position of an ending under observation can be roughly localized by pressing on the muscle with a glass rod and by local warming with an electrically heated pad while the muscle is subject to stretch. If this be done a region can be localized in many preparations where pressure produces the maximum response, and heating causes the greatest acceleration in the response to steady stretch. The method admittedly gives only very rough localization, but it is found that in general the receptors yielding the A 1 type response lie in the belly of the muscle, and in many cases they have appeared to lie near the top insertion of the muscle but never in the tendon.

In conclusion all the properties of the A 1 receptors certainly suggest that they are endings lying in the muscle spindles.

A 2 *type of response.*

The behaviour of these endings to passive stretch is practically identical with that of the A 1 type endings, though they often have a considerably higher threshold and the response rate rises more slowly with tension than does that of the A 1 endings; the chief difference in their behaviour lies in their response during tetanic contraction. Endings of this type form about 25 p.c. of those examined.

The difference between A 1 type of receptors and the A 2 type becomes clear when the strength of the stimulus evoking a motor response is varied. If the nerve be tetanized with submaximal shocks the cessation of response to stretch occurs as with the A 1 endings, but if the stimulus is made supramaximal the response is greatly accelerated during contraction. Behaviour of this sort has been observed in the frog [Matthews, 1931*b*] and ascribed there to contraction of the intrafusal muscle fibres occurring only with supramaximal stimulation; the same explanation fits the present observations very well.

The behaviour of an A 2 ending in peroneus longus is shown in Pl. I, Fig. 11 A and B. In B the stimulus is 15 p.c. submaximal, in A it is 10 p.c. supramaximal; thus an increase in the stimulus of a few per cent. completely transforms the end-organ's response, so that during contraction instead of the response stopping it is enormously accelerated. When the contraction is over the response rate in A falls below its original value;

presumably this is largely due to the adaptation brought about during the period of rapid response.

In Pl. II, Fig. 12, the behaviour of an A 2 ending in soleus is illustrated. The top records show the start of isometric tetanic contraction; in A the stimulus is just maximal, in B it is 20 p.c. supramaximal, in A the response to stretch ceases when the muscle contracts, in B it is accelerated. These phenomena are still more striking if during steady tetanic contraction the stimulus be increased from maximal to supramaximal. This is shown in Pl. II, Fig. 12 C; there is no visible increase in the strength of contraction with the increase of stimulus, but the end-organ formerly quiescent begins to respond. The conclusion of tetanic contraction with supramaximal stimulation is shown in Pl. II, Fig. 12 D. The continuity of the response during and after contraction (see also Pl. I, Fig. 11 A) leaves little doubt that the impulses occurring during contraction come from the same ending as those set up in response to passive stretch.

When the muscle is subjected to supramaximal stimulation at various initial lengths the response rate during contraction increases with the total tension in the muscle, and the response always occurs at a higher frequency than it does at the same external tension if the muscle is not contracting; with barely maximal stimulation the response frequency is far below that set up by the same passive tension. This is illustrated in Pl. II, Fig. 13. In A the nerve is tetanized supramaximally and the muscle extended until a tension of about 300 g. is reached, in B the stimulus is barely maximal, and in C the muscle is passively extended until the same tension is reached. The response rate in A is always higher, and that in B lower, than that in C.

Interpretation.

Thus the response of the end-organ is enormously dependent on small changes in the strength of stimulus applied to the nerve, though these do not produce any visible change in the total tension in the muscle. The most satisfactory interpretation of these observations is as follows. (*a*) That the A 2 ending lies in the muscle spindle; this is suggested by its behaviour during stretch and its "in parallel" behaviour during submaximal contraction. (*b*) That the threshold of the nerve fibres to the intrafusal fibres of the spindle is higher than that of the other motor fibres; this is in accord with the anatomical fact that these fibres are smaller [Ruffini, 1898], and Gasser and Erlanger [1925] have shown small fibres to be less excitable than large ones. When the threshold of the intrafusal motor nerve fibres is passed the nerve ending instead of

lying in a passive structure "in parallel" with those producing the tension, is stimulated by the contraction of the intrafusal fibres. This stimulation would seem to be mechanical rather than electrical or chemical, for firstly from A 2 endings there is as a rule no response if the muscle contracts with its tendon unattached whatever the strength of stimulus may be, and as the chemical and electrical changes will still be occurring in the intrafusal fibres we must assume that they have little or no stimulating effect; secondly the rate of response during supramaximal tetanus is related to the external tension developed. So it appears that the acceleration of response during contraction may be due to the nerve ending lying in effect in series with the contracting intrafusal fibres.

In one preparation when the tendon was freed and the nerve stimulated supramaximally, each stimulation escape in the electrical record was followed by two or three impulses in close succession which were apparently travelling in the same fibre as that carrying stretch impulses. These did not appear if the muscle was under tension (when the response was like that of Pl. II, Fig. 13 B) and they did not occur when the stimulus was made submaximal. They might certainly have been due to excitation of the nerve ending by the action current of the intrafusal fibres, and their absence under tension may have been due to the decrease in excitability of the ending with adaptation to the tension. These impulses have only been observed in this one preparation (though all were examined in this way), and their absence in other preparations and in this one during stretch makes it unlikely that such impulses have any great reflex importance.

Response of the A 2 *endings during twitch.*

In Fig. 14 A and B is shown the response of an A 2 type ending in peroneus longus during isometric twitch; in A the stimulus is 85 p.c. maximal, in B it is 10 p.c. supramaximal; as in tetanic contraction, a slight increase in the stimulus causes the pause in the response to be replaced by a rapid discharge of impulses. The maximum rate of response occurs before the maximum tension is reached. In Fig. 14 C and D are shown records of the response of A 2 endings in soleus when it contracts isometrically at two initial tensions, in both cases in response to supramaximal stimulation. At the lower tension there is a pause in the response, at the greater there is an acceleration during twitch. At the higher tension if the stimulus be submaximal the pause occurs as it does with A 2 endings in peroneus longus at all tensions (see Fig. 14 A). Some light is thrown on this behaviour by the response during supramaximal tetanus at moderate tensions (Pl. II, Fig. 12 B); here the response is increased in rate during steady tetanic contraction, but only after the tension has risen to its new value, the first twitch in the tetanic series in Fig. 12 B leading to a cessation of response which is clearly similar to

that in Fig. 14 C. At greater initial tension the increased response is established at once during the first twitch of the tetanic series. This is shown in Pl. I, Fig. 11 C, and is similar to the behaviour during isolated twitch in Fig. 14 D.

Possible explanation.

It has been suggested from observations of the response during sudden stretch and release that the end-organ structure, particularly in soleus,

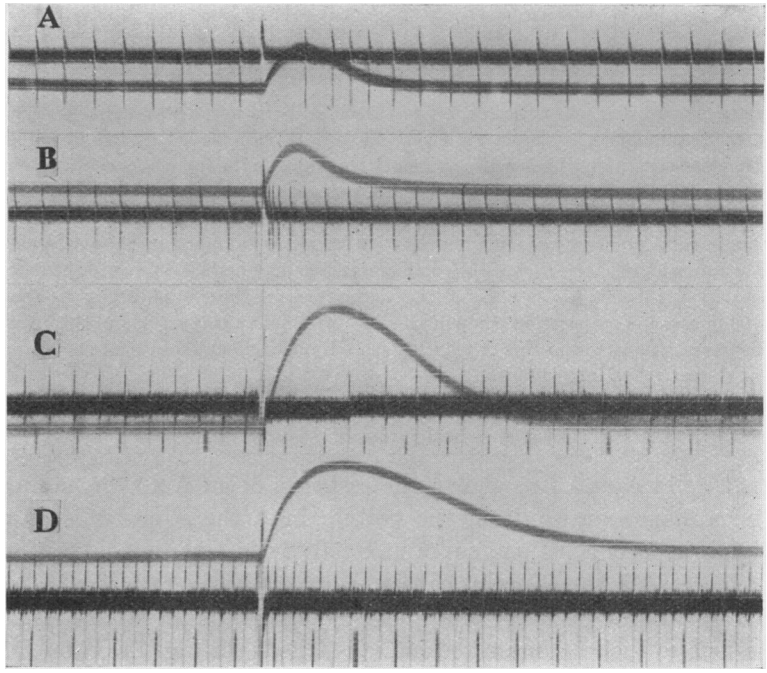

Fig. 14. Response from A 2 endings during twitch. A, B, peroneus longus, same ending, initial tension 40 g., stimulus 85 p.c. maximal in A, maximal in B. C, D, soleus 110 p.c. maximal stimulation, tensions 50 and 300 g. Time marker 1/20 sec.

may be more viscous than the rest of the muscle. That the viscous elastic properties of the intrafusal fibres may differ from those of the other muscle fibres is also suggested by their histological appearance; they are much finer and more coarsely cross-striated and contain very many nuclei. If this be so these results are very simply explained on the following lines. When the muscle contracts at moderate initial tension shortening will occur owing to the elastic yield of the tendon. Assuming

that with supramaximal stimulation the intrafusal fibres are contracting, we should expect a fall in the tension in the end-organ at the start of tetanization owing to the muscle as a whole shortening faster than the more viscous end-organ. Thus the response should at first cease or be reduced, and only rise to its new value after some time when the intrafusal fibres have shortened the same amount as the rest of the muscle. On the other hand at high tension the elongation of the tendon is negligible during twitch, so we might expect these effects of shortening to be absent.

Isotonic contraction.

If the muscle contracts isotonically the response ceases entirely if the stimulus be barely maximal; if the stimulus is supramaximal this still occurs as a rule, but in some preparations at all tensions, and all preparations at high (above 1000 g.) initial tensions, the response continues during isotonic tetanic contraction, though at a rate far lower than that set up before contraction. During isotonic twitch the pause is always absolute.

Response on relaxation.

From Pl. I, Fig. 11 A and B, it will be seen that during relaxation from isometric tetanus the response depends on the strength of the previous stimulus. On the view put forward above in Fig. 11 B the intrafusal fibres are passive, so that at the end of contraction the *status quo* at the nerve ending is restored and the response goes on again at its old level; on the other hand in Fig. 11 A and 12 D the intrafusal fibres are supposed to be actively contracting, and during tetanus their contraction will have caused them to shorten, so that on relaxation they will be re-extended. It will be seen that during relaxation the response is greater than it was before contraction, and this may perhaps be ascribed to this re-extension. Similar behaviour is seen on cessation of isotonic tetanus; if the stimulus has been barely maximal the response is far less during relaxation than if the stimulus has been supramaximal, though in both cases there has been little or no response during the contraction. This again may perhaps be ascribed to re-extension of passive or actively shortened intrafusal fibres.

Sharpness of change in response.

In all preparations of A 2 endings in peroneus longus and about two-thirds of those studied in soleus the change from silence to response during tetanization occurs very sharply, being produced by an increase of 1–2 p.c. in the stimulus, fine gradation of the stimulus failing to show

up any intermediate behaviour; moreover, the change often did not occur until the stimulus was supramaximal as judged by the height of contraction. But in about one-third of the soleus A 2 preparations the

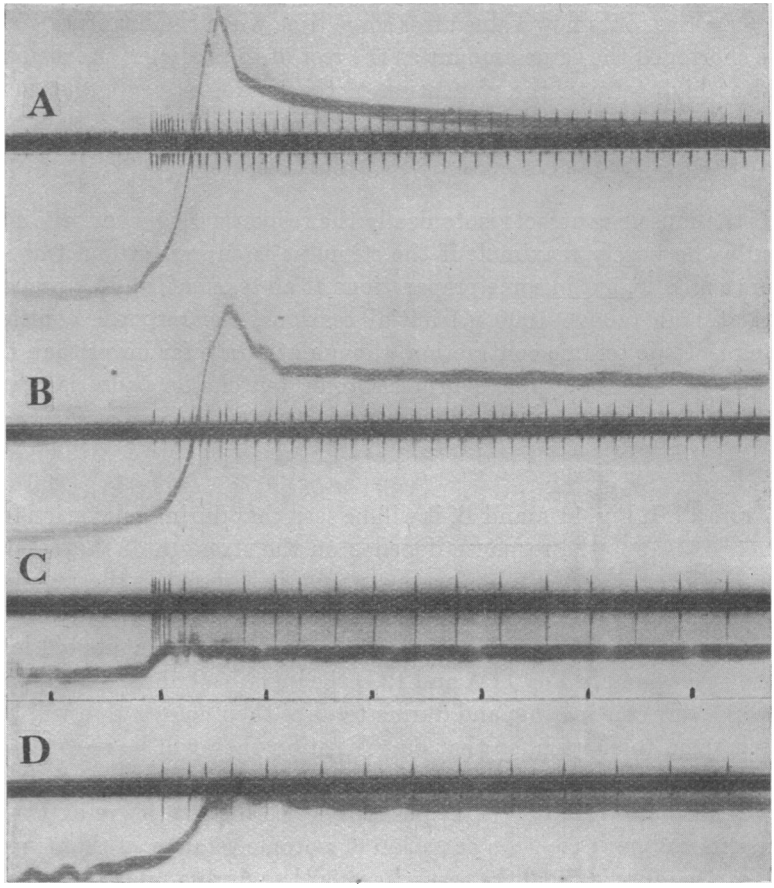

Fig. 15. Responses from A 1 and B endings in peroneus longus during rapid stretch. A, A 1 ending, extension 30 mm. per sec., final tension 35 g. B, B ending, extension 30 mm. per sec., final tension 140 g. C, A 1 ending, extension 50 mm. per sec., final extension 10 g. D, B ending, extension 50 mm. per sec., final tension 60 g. Marks at foot of C indicate 1/10 sec. intervals.

change in response occurred before the contraction had become maximal and took place gradually as the stimulus was increased, with several intermediate stages between complete silence and full response. In these preparations the changes usually occurred as the stimulus was increased

from 70 to 90 p.c. maximal. This behaviour might be due to the intrafusal fibres in the spindle contracting severally, as it is known that in some cases several motor nerve fibres enter the spindle.

The B, C *and other endings.*

The B endings have been found in every muscle that has been examined. About 25 p.c. of the single receptors examined have been of this

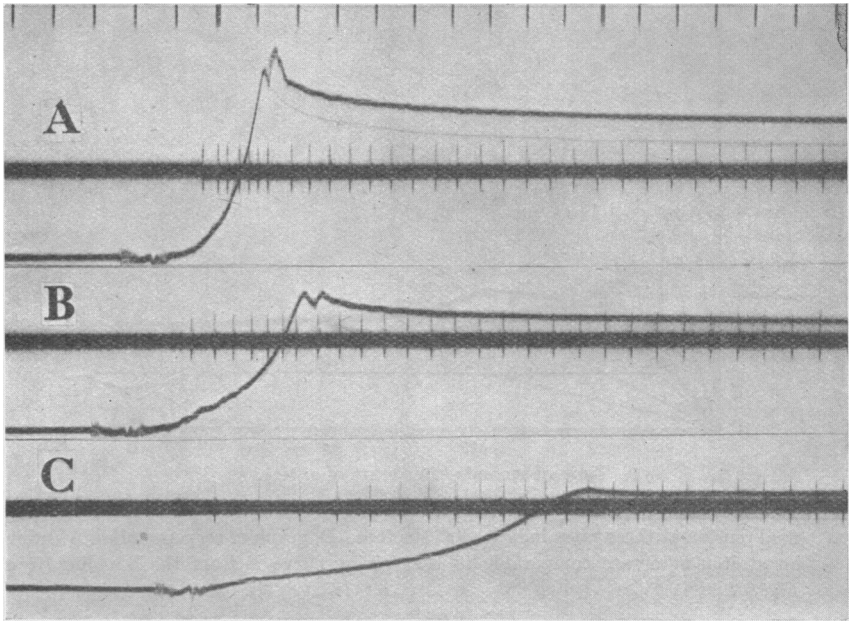

Fig. 16. Responses from a B ending in soleus. Stretch at three rates to a final tension of 260 g. Time marker 1/20 sec. at top.

type. They are very easily distinguished from the A endings by their behaviour during sudden stretch, for they do not give the rapid response characteristic of the A 1 and A 2 endings, and as a rule they have a far higher threshold; as a result they can be instantly distinguished by ear from the response in the loud speaker. The response during active contraction is also quite different from that of the A endings, for they respond as though they lay "in series" with the contracting elements whatever the strength of stimulus evoking contraction.

Response to stretch.

In Fig. 15 B and D are records from one of these endings in peroneus longus during rapid stretch, comparable records from A endings being shown in Fig. 15 A and C; Fig. 16 shows records from a B ending in soleus during stretch at various rates. Comparison with Fig. 5 reveals a striking difference in behaviour, for the response of the B ending seems to depend on the tension at any moment and to be only slightly affected by the rate

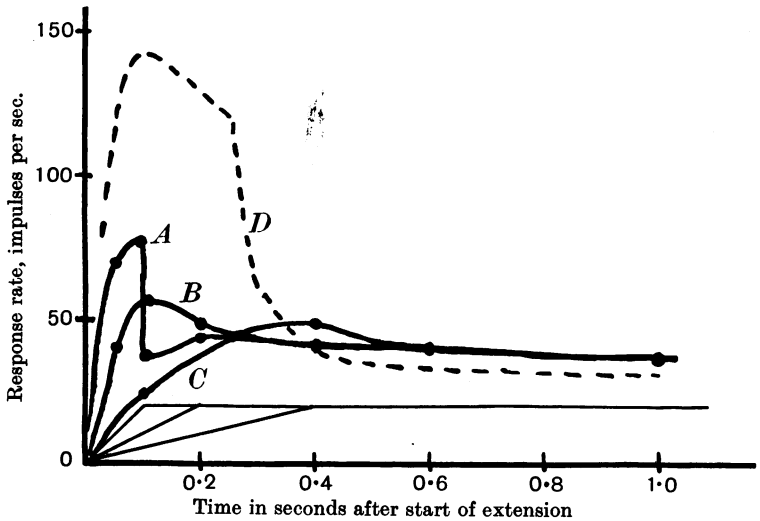

Fig. 17. A, B, C, graphs of response from a B ending in soleus during stretch to the same final tension at three rates indicated at the foot. D, graph of response of an A ending on stretch at a rate comparable to that giving curve B from the B ending (from Fig. 6).

of stretch, whereas that of the A ending is largely dependent on the rate of stretch. The response from a B ending in soleus stretched at various rates is shown graphically in Fig. 17, and one of the graphs of Fig. 6 from an A ending is redrawn to emphasize the very great difference in their behaviour. The behaviour of the B ending on quick release shown in Fig. 8 A also differs markedly from that of the A ending, in that the fall in the response rate is less marked, and the return of response follows more nearly the return of tension in the muscle after release.

Threshold.

The threshold of these endings in many preparations is far higher than that of A endings, which often respond in the absence of external tension

and always respond to a tension of 5–10 g. The B endings have never been found to give a response in the absence of external stretch, a tension of 20–200 g. usually being applied before the response begins, and in some preparations the threshold has been as high as 700 g. These endings can respond rapidly if the muscle is subjected to very high tensions, 5000 g.; but the rapid response suddenly falling to a much lower rate at the conclusion of the movement of extension cannot be evoked from them (the fall in Fig. 17 A correlated with the fall in total tension after rapid stretch). This strongly supports the view put forward above that this behaviour of the A endings is due rather to their anatomical position than to any common property of nerve endings.

Adaptation.

The adaptation curves of B endings are essentially similar to those of the A endings, but the phenomena noted above with A endings at high tension, that the response after falling slowly for a minute or more may suddenly stop or undergo transient acceleration followed by abrupt stop, are far more in evidence. If these phenomena be due to the effects of restriction of blood supply, this is to be expected, for the higher tensions necessary to stimulate these endings may produce a very great hindrance to the circulation.

Response during contraction.

The response during twitch at various initial tensions is shown in Fig. 18, and in Fig. 19 are records taken during maximal tetanic contraction, in A at low initial tension (soleus), in C at high initial tension (peroneus longus), and in B during steady contraction at various tensions evoked by maximal stimulation at various extensions. The records are similar to those in Fig. 19 B if the different tensions are produced by altering the stimulus at constant (considerable) stretch, though in a number of preparations as the stimulus is reduced the response drops out at a higher tension than it does if the extension is reduced with maximal stimulation. When the muscle contracts isotonically the response is unchanged or may accelerate by a few p.c. It will thus be seen that these endings always behave as though they are in series with the contractile elements, the response depending simply on the total tension in the muscle whether this be produced by active contraction or passive stretch. This is emphasized if the response is recorded during slow passive extension to considerable tension and also when the muscle is tetanized and gradually extended; the rate of response at any tension is

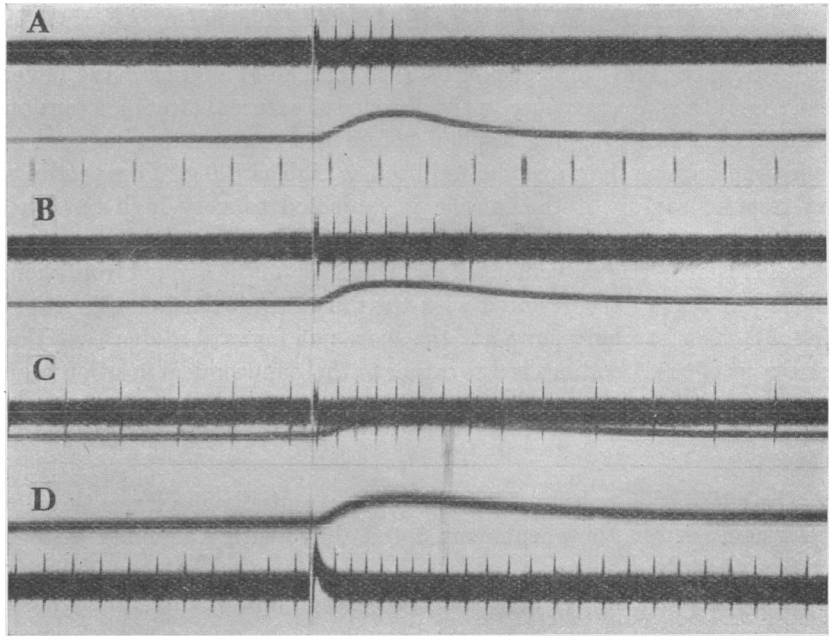

Fig. 18. Response from a B ending in soleus during maximal isometric twitch. A, B, C, D, initial tensions of 40, 130, 240, 600 g.

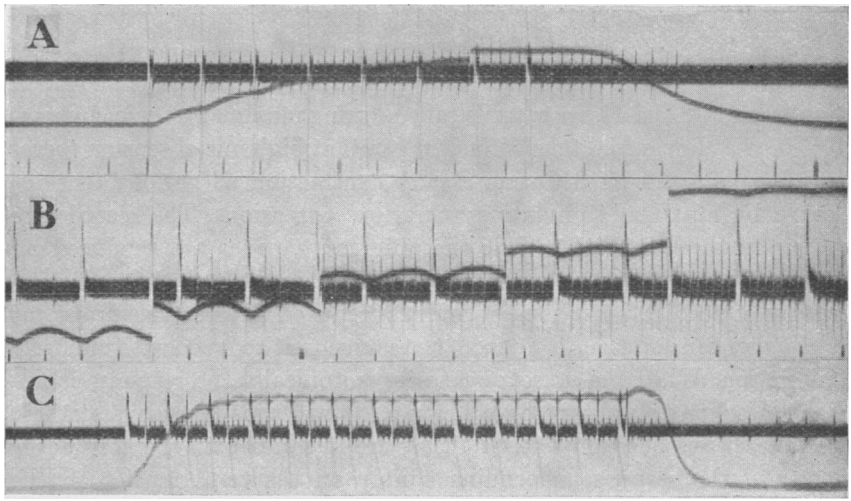

Fig. 19. Responses from B endings during maximal isometric tetanic contraction. A, soleus, initial tension 50 g. B, soleus, five records during steady tetanus, final tensions 50, 240, 470, 620, 950 g. C, peroneus longus, initial tension 80 g. Time marker 1/20 sec. at foot of A.

practically the same in the two cases, and in some preparations it is a little higher during active contraction, but there is never any great difference.

The above observations point strongly to the conclusion that the B endings lie in the attachments of the muscle and may be the tendon organs of Ruffini. Investigation of the position of the B endings by the warming and pressure methods described above accords with this view. In two cases B endings were clearly located in the tendon of the muscle (soleus); some appear to lie near the top insertion of the muscle, but the majority appear to lie in the muscle towards the tendon end. Ruffini's tendon organs are known to be present in these sites.

The C *type endings.*

These endings have only been met with in a few preparations. They do not appear to lie in the muscle but rather in the fascia associated with it, particularly that of peroneus longeus; if the fascia be cleared away the C type of ending is never found, and it has never been found to occur in soleus when cleared from its neighbours. Response from these endings occurs during stretch when 5–20 impulses are set up at a rate depending on the speed of stretch, but there is no continued response to steady tension, often a brief discharge occurring if the muscle is suddenly released from considerable extension.

During active contraction the behaviour of C endings is very variable, and they never give any continued response during contraction; often a group of 2–5 impulses is set during the rise or fall of mechanical activity, sometimes during both. But from the small numbers in which they are present it is unlikely that their response can have any considerable central effect.

Other types of response.

In a few preparations endings have been met with that do not fall sharply into the above classification (some 4 p.c. of those examined); to stretch they behaved as A endings, but during contraction of the muscle their behaviour did not justify their classification as either A 1 or A 2, for though they always continued to respond during contraction the response slowed during contraction by variable amounts that had no clear relation to the tension on the muscle, no small alterations in the motor stimulation having any effect on the response. In two preparations slight acceleration occurred on contraction whatever the strength of stimulation, but its magnitude was not related to the tension on the muscle. These endings may perhaps have been A 1 or A 2 endings which behaved abnormally owing to some peculiarity of their attachment in the muscle.

No endings have ever been found that have responded to active contraction and not to passive stretch.

Time relations of impulses.

A full study has not yet been made of the time relations of the action currents from the A 1, A 2 and B muscle receptors, but some results of interest are already to hand. For these time relations to be compared it is imperative that impulses from each receptor be recorded successively from the same electrodes on the same stretch of nerve, otherwise many disturbing factors enter and make comparative measurements impossible [see Matthews, 1929*b*]. Thus to study this point it is necessary to make preparations from which the response of two receptors of different types can be recorded. With the nerve-section method of isolation this is solely a matter of trial and error; moreover, care must be taken to see that the two surviving sensory fibres are not damaged and are both conducting beyond the recording electrodes, otherwise the action potentials will be distorted. Such preparations have been made, and from high-speed records (taken with 0·25 μF coupling condensers in the amplifier) the time relations of the action currents accompanying impulses from the A 1 endings appear to be slower than those from either A 2 or B endings.

In making single-ending preparations many two-ending preparations have been made and examined. Records taken with the 0·001 μF condensers usually employed give some indication of the comparative time relations of the action potentials recorded monophasically, for the faster potential changes give records of greater amplitude than slower potential changes which are more reduced by distortion (in some experiments 0·0005 μF condensers were used to this end). Thus the comparative heights of the deflections recorded give some indication of the rapidity of the process occurring, and providing that conduction of the fibres concerned up to the crushed region is verified by moving the electrodes (with monophasic recording decreased height of deflection might occur if the impulse is not conducted far beyond the first electrode) this indication should be quite reliable.

Records from preparations of two end-organs taken in this way are shown in Fig. 20. In I and II records from two B receptors are shown; in II the basic stretch is sub-threshold for both; in I it just causes one to respond. The amplitude of the deflection of the action potentials from both receptors is the same, and it may be concluded that they are transmitted by fibres of similar characteristics; this is always found to be the case with preparations of two similar endings. In III is a record from a preparation of one A 1 and one B receptor; the stretch is sub-threshold for the latter, but causes a vigorous response from the A 1 receptor, which ceases during

twitch and is replaced by the response from the B receptor (cf. Figs. 9 and 18), the much greater amplitude of the B impulses indicating that their action potentials are more rapid than those of the A 1 impulses. Similar records of impulses from A 1 and A 2 receptors show those from the latter to be travelling in fibres of faster characteristics than are the former. It thus seems very probable that the A 1 impulses travel in smaller fibres than do impulses from the A 2 or B receptors. No reliable

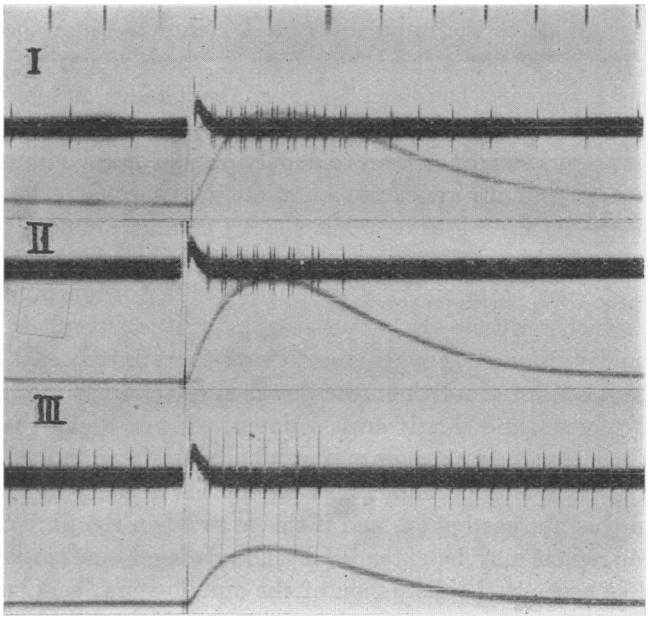

Fig. 20. Records of impulses from two receptors in the same preparation, during isometric twitch of soleus. I, II, two B type receptors, initial tensions 100 and 40 g. III, one A 1 and one B receptor, initial tension 40 g. Time marker 1/20 sec.

records have been made from A 2 + B preparations, so it is impossible to say whether fibres to these endings have identical characteristics, but the order of differences between A 1 and A 2 and A 1 and B impulses is similar, and so A 2 and B impulses cannot be very different.

Nature of the receptors.

We will here examine what correlation there is between the response of the stretch receptors and the known histological structures present in muscle. Evidence presented above (their "in series" behaviour, etc.) suggests that the B response comes from the tendon organs and the A 1

and A 2 response from endings (their "in parallel" behaviour, etc.) in the muscle spindle. Two histologically very different types of ending are present here, the flower-spray and annulo-spiral endings. For the reasons given below it is thought that A 1 response comes from the flower-spray endings, and the A 2 response from the annulo-spiral endings.

(*a*) Histological examination [*e.g.* Ruffini, 1898] shows the flower-spray endings to be supplied by medium sized nerve fibres, while the annulo-spiral and tendon organs are supplied by unusually large fibres. The time relations of the impulses from A 1 endings show them to be travelling in smaller fibres than those from A 2 or B receptors.

(*b*) The A response has been found in about twice as many single-ending preparations as the A 2 response. More fibres enter the spindle to supply flower-spray endings than to supply annulo-spiral endings.

(*c*) The A 2 endings appear to be stimulated mechanically by contraction of the intrafusal fibres, while the A 1 endings are not. Both A 1 and A 2 endings are stimulated by tension, which presumably acts by the distortion of their parts which it produces, for distortion produced by prodding a flaccid muscle also stimulates them; it is difficult to see how tension could stimulate except by the distortion it produces. The regions of the intrafusal fibres on which the flower-spray endings are found are apparently normal and clearly cross-striated, whereas under the annulo-spiral endings the fibres are poorly if at all cross-striated and are packed with nuclei. It seems probable that contractile activity is poorly developed in this nuclear region, and if this is so when the fibre contracts the nuclear region may be extended by the stronger contraction of the ends, and as a result the distortion of the annulo-spiral endings will be greatly increased while that of the flower-spray endings will be decreased. If this interpretation is correct the observed differences in their behaviour are clearly accounted for.

It thus appears very probable that the A 1 response is that of the flower-spray ending in the spindle, the A 2 response that of the annulo-spiral ending, and the B response that of the tendon organ. There are no observations that do not accord with this view.

Reflex effects.

An examination of the phenomena of the silent period makes it possible to suggest tentatively what the central effects from the various receptors may be.

In a previous paper [Matthews, 1931*b*] it was suggested from observations on the frog's spindles that the disappearance of stretch reflex

action currents from muscles which occurs during twitch evoked by either reflex or direct stimulation, might result from the cessation of response of the receptors normally evoking it. That this will play a part in the phenomenon seems inevitable, but observations [Cooper and Creed, 1926, 1928; Denny Brown, 1928] that not only do the stretch reflex action currents disappear from the muscle stimulated but also from associated muscles that have not contracted indicate either that during twitch impulses producing inhibition of the stretch reflex in other muscles are set up, or else that exciting impulses from one muscle contribute to the excitation of the centres of other muscles; there is no other evidence to support the latter alternative and the highly localized nature of the stretch reflex makes it improbable, and the former is supported by reflex behaviour.

There is thus reason to believe that during a twitch inhibitory impulses are set up; these impulses must be those coming from the B endings, for impulses only from these occur under all the conditions in which the silent period is in evidence. This is clear from the following considerations. The silent period is most in evidence at low basic tensions, and under these conditions the A 2 endings in soleus do not respond during twitch even if the intrafusal fibres contract (see Fig. 14 C). The A 1 endings never respond during twitch (Fig. 9), only the B endings respond during twitch at low tension (Fig. 18). So these alone can be held responsible for the inhibition. That B endings may produce inhibition agrees with the well-known cessation of stretch reflex that occurs when a muscle is stretched violently, and under these conditions the B receptors will produce a considerable response, but at lower tensions owing to their high threshold their response will be slight or absent.

The function of the A 1 endings appears to be excitation of the stretch reflex. The A 2 endings may also excite this reflex, but the very low threshold and numerical preponderance of the former suggest that they will be the dominating influence in this. If this is so, the silent period appears to be due both to the absence of excitatory impulses from the A 1 (and perhaps A 2 endings) and to the inhibitory impulses set up by the B endings. Fig. 20 III illustrates this point very clearly. During twitch, the supposed excitatory impulses from the A 1 ending cease, and the supposed inhibitory impulses are set up by the B ending.

If the time relations of impulses play a part in determining their central effect, there are differences between those of the exciting A 1 impulses and inhibitory B impulses amply sufficient to account for their very different central effects. But the time relations of A 2 and B

impulses are very similar, so if these determine the inhibitory effect of B impulses, the A 2 impulses should also produce inhibition. This may indeed be the case, but there is no possibility of a decision on this point until we know under what conditions of central excitation the intrafusal fibre contracts, for the response of the A 2 endings is entirely dependent on this. If the A 2 impulses are inhibitory we must imagine that in a stretch reflex a balance is struck between excitation and inhibition in favour of the former, owing to the greater excitability and number of A 1 receptors. During twitch this excitation and inhibition will both cease and be replaced by the B ending inhibition. What will happen in tetanic contraction depends entirely on the intrafusal fibres; on the whole a balance in favour of inhibition might be anticipated, so that a contracting muscle would always tend to inhibit its own contraction! It is clear that evidence of the central exciting or inhibiting effect of A 2 endings must come rather from observations on reflex effects. From the present work A 2 impulses might be either inhibiting or excitatory; the evidence above is slightly in favour of their being inhibitory, and existing reflex evidence also suggests this conclusion.

Part III. Factors affecting the response of stretch receptors.

Effects of circulatory arrest.

The effects of arresting the circulation to the muscle on the response of end-organs lying in it are extraordinarily interesting, for not only do they shed some light on the mechanism of the end-organ, but they are also of interest in connection with the intense muscular pain that occurs in limbs with occluded circulation that has recently been studied in detail by Lewis, Pickering and Rothschild [1931]. The effects observed here depend to some extent on the state of the animal, as there are considerable differences in these effects in spinal, decerebrate, and anæsthetized animals. The effects in decerebrate animals will be considered in greatest detail, as these are in a state most nearly approximating to that of the living animal.

Decerebrate animals.

In decerebrate animals it has been found a matter of some difficulty to stop the circulation by clamping the arteries, as owing to the high blood-pressure (as compared to spinal animals) collateral circulation which is difficult to locate is often quite effective in maintaining the blood supply. The methods used to arrest the circulation have been, clamping the femoral artery where it leaves the abdominal cavity, clamping the arteries

as close to the muscle as is practicable, and tying a cord tightly round the thigh.

Many of the A 1 and a few A 2 endings respond with the pulse, and at each heart beat one or two impulses are set up when the muscle is slack. This response vanishes instantly on clamping the arteries, but no other immediate change occurs in the behaviour of the nerve ending; it thus appears that the blood-pressure does not have any appreciable mechanical effect on the end-organ.

If the circulation is arrested, and precautions are taken to prevent cooling of the limb, the response to stretch from a single nerve ending of any of the types described at first increases up to 20 p.c. or less, then it becomes gradually smaller until after 5–20 min. there is only a brief response when the muscle is extended. During this period of lowered excitability the ending will still set up a continued response when a very large load is applied to the tendon. After a further lapse of some minutes the response returns and increases, so that a given stretch sets up a greater and greater discharge; after half an hour of hyperexcitability the response to stretch gradually becomes less and less but may be still present 1½ hours after the occlusion of circulation. A resting discharge in the absence of stretch also appears as the hyperexcitability develops, and it retains the characteristic of the normal resting discharge that after stretch it stops or is at least reduced in frequency. In a few preparations this discharge has risen to a rate of about 50 per sec. After this occurs it rises rapidly to a rate of 300–400 per sec., and after it rises above 300 per sec., with this high rate of discharge, stretching the muscle causes only a slight acceleration, and there is only a slight slowing on release. The discharge continues at 300–500 per sec. for 1–4 min. and then falls rapidly, and after a few seconds' irregularity ceases abruptly. No further response can be evoked by stretch. If the circulation is now released after 2–10 sec. the rapid response suddenly restarts and falls to extinction in 1 or 2 sec.; after a few minutes' rest the end-organ is once more in its original condition and the whole sequence of events may be repeated.

Occlusion and motor stimulation.

The sequence of events described above occurs far more rapidly and the rapid spontaneous response occurs in every preparation if the muscle is stimulated *via* the nerve after occlusion of the circulation; 1 min. tetanization is often sufficient to bring on the spontaneous rapid response. If this tetanization is applied in 5 sec. bursts, at intervals of 10 sec., and after each the state of the end-organ be examined by recording its

response to stretch, it is found that the excitability of the ending changes in the same way as it does after occlusion without stimulation but far more rapidly. The response under these conditions is shown graphically in Fig. 21; the full line shows response to steady tension, the dotted curve shows the result of repeating the experiment with no tension on the tendon. When the response reaches a frequency of about 100 per sec., even without further stimulation, its rate rises rapidly to 350–500 per sec. and is

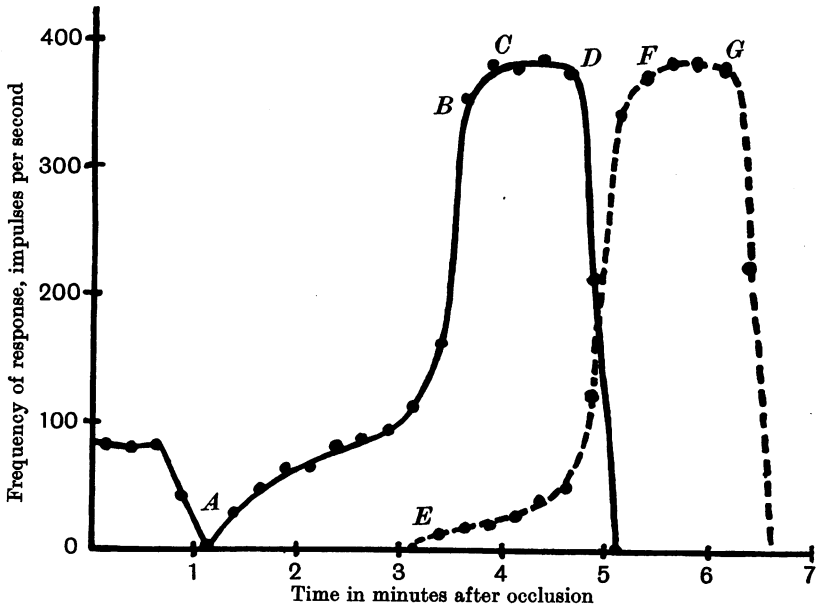

Fig. 21. Graph of response from an A 1 ending after occlusion of the circulation. The nerve is tetanized for 5 sec. at 20 per sec. every 15 sec. The full line shows the response when 50 g. tension is maintained in the tendon, the dotted line that occurring if the muscle slack.

maintained for 1–4 min. before it fails; but with preparations in which a number of endings are under observation, after a burst of stimulation that initiates the spontaneous discharge from some of the endings present, though the response from these rises to a maximum and after a few minutes fails, new endings are recruited to the spontaneous discharge slowly, whereas further stimulation will initiate the rapid response from a large number of endings not previously responding spontaneously. When the response of the whole nerve is observed, after each burst of stimulation a number of endings "explode," but the total response does not increase further until after a further burst of stimulation and may even die down after a few minutes. The first nerve endings to "explode"

do so before the mechanical response has fallen noticeably (from fatigue), the last often do not "explode" until the contraction of the muscle has become feeble.

These observations suggest that some factor accumulates on stimulation, which causes the excitability to rise and initiates the spontaneous response, but that the course of this response once started is determined by the activity itself rather than by further changes in the excitability brought about by the initiating factor; for after stimulation the response of an ending which has begun to respond spontaneously rises rapidly, though the exciting factor does not seem to be increasing sufficiently to recruit other endings immediately.

That this may be so is supported by the following observations. If an ending behaving like that in Fig. 21 have the stretch stimulus removed at any point B–C the response falls immediately but then continues to rise and the rapid response occurs earlier and thus after less stimulation than it does if the stimulus, and therefore response, be absent during the period AB; so the attainment of the spontaneous response state is accelerated by the activity during this period. Secondly, if the muscle is unloaded at C the rapid response continues and its termination is unaltered so that it must result from the activity A–C, for if the muscle be unloaded at A the response follows the course EFG, therefore the failure at D appears to result from the activity A–C. Thus though the preliminary changes in the excitability are due to the lack of circulation, the course of the final rise and extinction is determined rather by the activity of the nerve ending which appears to initiate a self-destructive activity.

If the circulation is released immediately after the failure of an ending the rapid response restarts and falls quickly to zero in 1 or 2 sec.; but if after failure further stimulation is applied, this does not occur on release, but some minutes later the ending is found to have returned to its normal resting state.

If the circulation is released while an ending is responding rapidly, the response begins to fall rapidly 1–5 sec. later, and ceases after 1–3 sec., even if bursts of stimulation be still applied to the nerve.

Constancy of behaviour.

Although there are these variations in the attainment of the spontaneous discharge in different preparations, in any single-ending preparation the changes in the response after successive clampings of the artery agree very closely. When the time taken to reach the spontaneous response has once been observed, the moment when the response will begin and reach its height can be predicted within 10 sec. for future clampings, for if the muscle is allowed 10 min. rest after each series of observations the whole sequence of events is exactly repeated.

With the preparation in Fig. 21 the spontaneous discharge was rising rapidly 5 min. after occlusion with stimulation every 10 sec. for 5 sec.;

when the occlusion was repeated and continuous stimulation applied for 100 sec., on cessation the spontaneous response was again found to be rising rapidly; thus the incidence of the spontaneous response depends much more on the total stimulation that has been applied than on the time that has elapsed since circulatory arrest. This is found to be the case however the stimulation is spread out, though with prolonged occlusion the spontaneous response occurs with less stimulation than in brief occlusion, so that the time factor does also come in; this is also shown by the fact that in a few preparations the response has been obtained with no stimulation but prolonged occlusion.

When the behaviour of several identified endings in a muscle is examined it is found that the A 1 and A 2 endings give the spontaneous discharge sooner after clamping with stimulation than do the B type endings. Only three observations have been made on this; but they agree with the observation above that these endings have a high threshold to stretch and are presumably less excitable, and if as seems likely they are tendon endings they may well be less in the path of chemical changes occurring in the muscle than the endings in the spindles.

All stretch receptors behave in this way.

All the stretch receptors present in a muscle appear to go through these changes in excitability after motor stimulation. The response of the whole nerve can best be followed by ear with the loud speaker. When each ending producing a rapid response gives rise to a siren-like wail from the loud speaker, six or more spontaneous responses can sometimes be heard simultaneously; the maximum frequencies set up by the different receptors are of the same order but not identical, so that a number of notes are heard (from aural observations it is thought that these notes may fall into two groups, one of rather higher pitch than the other). When a further ending starts its spontaneous discharge a rising tone is heard very like that of a rotary factory siren starting up. By counting the number of these rising tones after each burst of motor stimulation it is possible to estimate the total number of endings in a muscle behaving in this way; in soleus about 40 "exploding" nerve endings can be counted after stimulation. After some minutes' stimulation all the endings present appear to have undergone "explosion," for there is no continued response even to large loads, and a few impulses are set up during extension only. A peculiar feature that has been noted in several preparations is that if during the spontaneous rapid response the muscle is violently (2000 g.) stretched the response ceases and recommences on release.

Spinal animals.

In these the spontaneous discharge is brought on with extreme ease, even without stimulation, often only a minute after occlusion if the nerve is not stimulated or after 10–40 sec. when it is. Moreover the spontaneous response appears sooner and sooner after clamping as time elapses after decapitation, and after 4–5 hours the endings seem to be in a hyper-excitable state even with uninterrupted circulation. The ventilation was not measured and was probably excessive, but even the ventilation necessary to ward off convulsions appeared much greater than that of a decerebrate animal. For these reasons spinal animals were not used in working out the details of end-organ behaviour described earlier in this paper. If the respiration pump is stopped spontaneous discharges begin with the onset of convulsions.

Anæsthetized animals.

With animals under urethane the spontaneous discharge has never been obtained. When the circulation is clamped, after brief hyper-excitability the endings become very unexcitable, and later the excitability rises above normal but never so high that the spontaneous response occurs even if the nerve is stimulated until the muscle has ceased to contract. Similarly if ether, chloroform or urethane is administered to a spinal or decerebrate animal, the spontaneous response previously occurring on arrest of the circulation cannot be made to take place. In several preparations during induction of chloroform and other anæsthesia a rise of excitability was found, indicated by a greater response to a constant stretch.

Discussion.

As a result of circulatory arrest the nerve ending undergoes great changes in its excitability, and this seems to be closly connected with the metabolic activities of the surrounding muscle, though as yet it is impossible to suggest what factor is responsible for these changes. The hyperexcitability found in spinal animals probably results from the excessive ventilation disturbing the balance of the blood in regard to this factor. Anæsthetics appear to reduce the susceptibility of the nerve endings to it, so that the spontaneous rapid discharge is impossible, but they only slightly affect the response to stretch, at first increasing it, later in deep anæsthesia it is a little reduced, but it is difficult to determine the origin of this effect since anæsthesia is also accompanied by changed

ventilation which probably in itself alters the end-organ response; in the extreme case of this, clamping the trachea of a decerebrate animal leads to spontaneous response in the endings in its muscles soon after the onset of convulsions; it does not seem unlikely that the convulsions may be intensified by the reflex effect of excessive impulses from hyperexcitable endings in the muscles.

The rapid discharges which occur in the absence of an external stimulus bear a remarkable resemblance to those recorded by Adrian [1930] from damaged nerve fibres, and suggest that as a result of muscular activity and lack of circulation, the nerve ending breaks down and allows its nerve fibre to behave as though it were cut. One of the most notable features of this phenomenon is that the whole process is reversible, and that recovery from such catastrophic changes in the nerve ending can occur quite rapidly.

The spontaneous discharge seems to originate in the end-organ or in some part of the nerve fibre very closely associated with it, for the rise of excitability as judged by the response to stretch and by the spontaneous discharge run parallel; the spontaneous discharge is evidently originating from the same region as the normal resting discharge and stretch response, for its frequency is reduced after stretching. When the spontaneous discharge reaches its height each impulse is set up very soon after the end of the absolute refractory period of its predecessor, and only then is the rate unaffected by stretch.

Since there is no reason to suppose that the end-organ differs essentially from other excitable structures, where it is generally supposed a propagated disturbance is due to a breakdown of a polarized surface, we may assume that tension on the end-organ stimulates it by deforming the surface membrane sufficiently to produce complete instability. The breakdown is followed by a refractory phase and gradual return of the membrane to its normal polarized condition, but the continued action of the stimulus causes a renewed breakdown as soon as recovery has advanced far enough for the stimulus to become effective. In a previous paper from observations on single receptors it was suggested that adaptation might be due to a depletion of some substance necessary for repolarization inside the membrane or its accumulation outside, leading to a slowing of the recovery process and so of the rate at which impulses are discharged. The observations in this paper are in agreement with the above view of the end-organ mechanism. Moreover, it is supported by the continuous change which occurs in the end-organ response when the circulation is arrested, from that proper to a nerve ending to that set up by a damaged

nerve fibre. We may suppose that the increasing excitability is due to some factor which accumulates on stimulation of the muscle, making the membrane more permeable and unstable until finally it becomes completely permeable and is virtually a cut fibre; the adjacent regions of the fibre then respond at a rate determined by their refractory period and rate of recovery, as those of a cut fibre are known to do. The instability resulting from muscular activity appears at first sight to be comparable to that produced by stretch. But some differences are evident, for while the instability and activity resulting from stretch are accompanied by slowing of the recovery process evidenced by adaptation and a slower response, the activity resulting from muscular contraction appears itself to increase the response rate. This might be due to the instability increasing so rapidly under these conditions that the effects of slowed recovery are swamped. The termination of the spontaneous response may perhaps be due to a total failure of other parts of the fibre in the end-organ occurring owing to the great activity. On readmission of circulation progressive repolarization appears to occur very rapidly.

If the nerve-ending membrane behaves like that of a nerve fibre, the above changes accord with effects observed in nerve fibres. Recent work on the after potential and retention of negativity in nerve [Amberson and Downing, 1929; Gasser and Erlanger, 1930; Amberson, Parpart and Sanders, 1931; Furusawa, 1929] has shown: (*a*) That reduced polarization of the nerve membrane is associated with hyperexcitability. Gasser and Erlanger found that the phase of supernormal excitability in recovery was present under the conditions which lead to the appearance of after potential, and that the two phenomena seemed to be inseparable. (*b*) That the passage of impulses reduces the membrane polarization, and can even depolarize it completely in crustacean nerve. (*c*) That such depolarization occurs readily in the absence of oxygen. (*d*) That oxygen appears to be necessary for maintenance of the polarization on which transmission of impulses depends, rather than for the actual transmission. Thus these phenomena observed in nerve endings can be accounted for if we assume that the polarized membrane of a nerve ending has all the properties ascribed to that of the fibre in greater or less degree. To explain the differences in adaptation of a nerve fibre and ending several assumptions are necessary, but some of these differences [see Matthews, 1931*b*] may well be connected with the fact that whereas in nerve fibres a symmetrical stretch of polarized membrane is observed, in nerve endings the fibre comes to an end and its modified behaviour may be due in part to its asymmetry, rather than to any fundamental differences in the properties

of its polarized membrane. There is no experimental evidence that justifies us at present in ascribing to the nerve-ending membrane properties not shared by its nerve fibre.

Possible central effects of the above phenomena.

It does not seem at all unlikely that great changes in the excitability of muscle receptors may occur during severe muscular work (similar to those occurring on activity with occluded circulation though lesser in degree) and may in part contribute to the central fatigue resulting from it.

The central effects of occlusion of the circulation to muscles have been studied in detail by Lewis, Pickering and Rothschild [1931], and they have shown that in man intense muscular pain occurs if a muscle is made to contract after circulatory arrest. The conditions that lead to this intense pain are exactly similar to those that lead to the spontaneous rapid discharge of impulses from the muscle receptors studied here. The most striking similarities of the phenomena are as follows: (1) Both the pain and the spontaneous response appear when a definite amount of muscular activity has taken place after occlusion. (2) On release of the circulation the pain vanishes very rapidly, so does the spontaneous discharge. (3) If the muscle has been contracting just before the circulation is arrested, the pain comes on with less activity than is necessary to elicit it if such previous activity has not taken place; this is also true of the spontaneous response. (4) On cessation of muscular activity the pain stops increasing and may fluctuate, but it rises with further activity; the total spontaneous discharge from all the receptors in a muscle also remains steady or falls a little when activity ceases and rises again on further activity. The phenomena appear to be exactly parallel, and we must conclude either that the same factor resulting from activity of the muscle affects both stretch receptors and pain endings in the same sort of way, or else that the rapid responses from stretch receptors are interpreted as pain. Lewis attributes the pain to an accumulation of "factor P" which results from muscular activity and stimulates pain nerve endings in the muscle, possibly the small fibres associated with the blood vessels are concerned; that occlusion and activity may affect the excitability of these in the same way is highly probable, and they may indeed be responsible for the pain. Discharges in fibres not carrying stretch impulses have not been detected in the nerves studied here, but they may well be present and pass undetected owing to the smallness of the potentials accompanying the activity of small fibres. However, it is very hard to believe that the enormous sensory discharge from the stretch nerve endings produces no

central effect, and it does not seem improbable that it might itself be responsible for the pain. It is most unlikely that such fundamental changes in the stretch receptors occur in the cat, and not in man, for these receptors are very similar; presumably the rapid response from the stretch receptors occurs in man, but if so it does not produce any obvious reflex contraction of the muscle, nor prevent its voluntary contraction; this might be due to a balance of excitatory and inhibitory effects, but this does not seem probable; thus the rapid discharge does not appear to be able to evoke reflex effects of the kind that are probably evoked by discharges at lower frequencies. If the discharges discussed here are responsible for the pain, then the same nerve fibres must convey impulses that have quite different central effects from those normally evoked by impulses occurring at lower frequencies in the same fibres; that this might occur accords with other observations on the central effects of sensory impulses discussed below.

There is a good deal of evidence that the size of sensory nerve fibres is related to the type of end-organs in which they end, and so to the sensations which they arouse [see *e.g.* Gasser and Erlanger, 1929]. In a previous paper [Matthews, 1929*b*] it was shown that cutaneous and muscular impulses in the frog were distinguishable from the time relations of their action currents. It is not unlikely that the time relations of impulses arriving at the C.N.S. in part determine their effect there and perhaps determine the paths that are open to them. For if the dendrites of second-order neurones vary in their excitation time characteristics, incoming impulses of particular time relations may pick out and stimulate particular second-order fibres.

If this is indeed the case we might anticipate that the rapid discharges described above would have central effects different from those of the normal slower discharges in the same fibres that subserve muscle sense, for during the rapid discharge each impulse is set up early in the relative refractory phase by its predecessor, and as a result the time relations of its action current will be considerably slowed [cf. Gasser and Erlanger, 1925; Matthews, 1931*a*]. Thus the electric responses of the impulses in the rapid response will be much slower than those of the impulses normally set up by stretch and will become more like those of the small fibres generally considered to transmit pain; this might well lead to their exciting different regions in the C.N.S. and interpretation as pain instead of as muscle sense. In this connection it is interesting that stimulation of a muscular nerve through the skin at 500 per sec. is extremely painful, and the pain has the character of that resulting from activity of muscles

with occluded circulation. Stimulation at 150 per sec., though unpleasant, is not very painful. These results are complicated by the contraction of the muscles resulting from stimulation, but certainly agree with the point of view put forward here that high frequency may in this case lead to impulses to be interpreted as pain.

However high frequency discharges in all nerve fibres cannot evoke pain, for Adrian, Cattell and Hoagland [1931] have shown that rapid intermittent stimulation of the skin does not elicit any sign of pain from an intact frog, though impulses at a high frequency are certainly set up under these conditions.

The effects of antidromic impulses on the stretch response.

A method which has been used to analyse the mechanism of diverse rhythmic structures is to observe how the spontaneous rhythm is affected by additional activity induced by electrical stimulation. This method has been used in the present work to examine the rhythm of the nerve ending. The effects of antidromic impulses on the stretch response have been studied in a number of preparations. The animal must be curarized to abolish the contraction of the muscles when the nerve is stimulated. To this end 1–2 c.c. of 1 p.c. curare in saline were injected intravenously, and 1–2 c.c. subcutaneously, for unless the subcutaneous injection was given the curarization was found to pass off slowly after ½–1 hour; artificial respiration was given. The curare has not been found to have any marked effect on the response to stretch.

Results.

It was found in the frog [Matthews, 1931*b*] that the end-organ response was "reset" by antidromic impulses, but these caused very little, if any, delay in the setting up of the next impulse by the rhythmic mechanism even if the antidromic impulse occurred early in the recovery cycle of the ending. But in the cat a considerable delay follows an antidromic impulse early in the cycle; the similarity of behaviour of the cat's and frog's receptors in other respects makes this difference the more surprising; no satisfactory explanation of this dissimilarity is at present apparent.

In the cat if a descending impulse is set up in the nerve, unless it meets an ascending impulse it apparently reaches the region of the end-organ that determines the rhythm, for this is "reset" and follows on from the descending impulse. This is illustrated in Fig. 22. Even if the descending impulse is set up immediately (0·002–0·003 sec.) after the arrival of an

ascending impulse the rhythm is reset, so this impulse must have reached the region determining the rhythm and activated it; thus under these conditions the absolute refractory period of this region cannot be of a very different order from that of the nerve fibre.

The length of the interval following a descending impulse depends on the position of this impulse in the rhythmic cycle of the end-organ, this may be seen in Fig. 22. In the top record where the descending impulse follows soon after an ascending one the succeeding interval is considerably

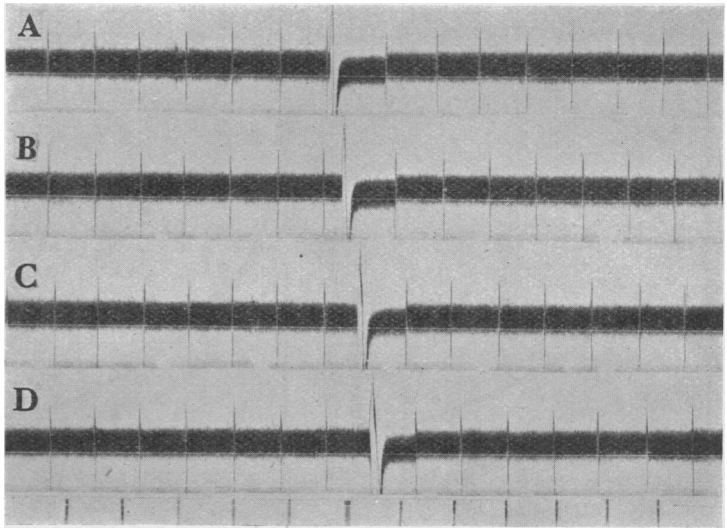

Fig. 22. Records showing the effect of antidromic impulses on the rhythmic discharge of an A 1 ending. In A–D this impulse occurs at different times in the rhythmic cycle of the nerve ending. Time marker 1/20 sec. at foot.

longer than in the bottom record, where the descending impulse occurs late in the rhythmic cycle. The interval following the descending impulse increases, as this impulse occurs earlier in the cycle. This is shown graphically in Fig. 23 at two rates of rhythmic response from the same nerve ending.

The pause following the descending impulse is made up of: (*a*) The time taken by this impulse to reach the rhythmic structure. (*b*) The time taken by the latter to recover sufficient excitability to set up an impulse in response to stretch. (*c*) The time this impulse takes to reach the recording electrodes. The conduction time (*a*)–(*c*) will be of the order 1–2 thousandths of a second and will be the same at any rhythmic rate.

(*b*), on the other hand, depends on the position of the descending impulse in the cycle and on the external stimulus (stretch).

Rate of response.

The graphs of Fig. 23 show the intervals measured from the records expressed as percentages of the mean rhythmic interval. Clearly to obtain the times of recovery of the rhythmic structure we must from these subtract the time occupied in conduction; if this is taken as 0·0015 sec. it forms 1 p.c. of the interval in A (rate 7 per sec.) and 11 p.c. of that in B (rate 70 per sec.). If we subtract 11 p.c. from the intervals in A and 1 p.c. from those in B the results will represent more nearly the recovery time of the rhythmic structure. The graph B has been lifted

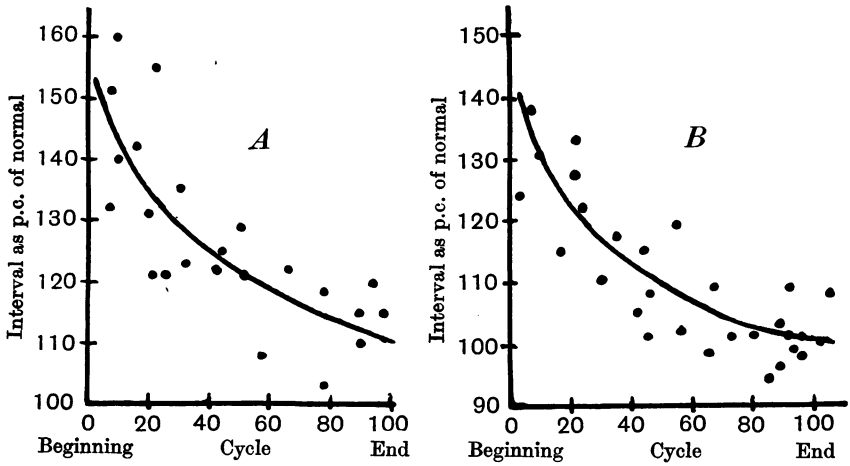

Fig. 23. Graphs of the interval following an antidromic impulse (expressed as a percentage of the interval of the rhythmic response) plotted against the position of that impulse in rhythmic cycle of the nerve ending. A, mean rate 70 per sec. B, mean rate 7·1 per sec.

10 p.c. relative to A for this reason, and it will be seen that the two graphs read on the ordinate of A are very similar. A similar correction for conduction time might be applied to the abcissa, but this has been omitted for simplicity. It is clearly impossible to activate the ending by a descending impulse until at least 0·0015 sec. has elapsed after its own activity; at a rate of 70 per sec. 10 p.c. of the cycle will thus elapse, and cannot be examined by this method.

It is clear that the recovery interval following a descending impulse (expressed as a percentage of the normal interval of the rhythm) varies with its position in the rhythmic cycle in roughly the same way at widely different rates of response, though at a slow rate the delay following the early descending impulse has a far greater absolute value.

It is found from a large number of measurements that after the prolonged interval following the early descending impulse the next interval is always normal.

Several antidromic impulses.

If a number of descending impulses are set up at a rate only slightly greater than those previously set up by the ending, the interval following the last before an ascending impulse appears is practically normal (quite normal if conduction time be allowed for). However, if the frequency of descending impulses is much greater than this ($\times$ 5) there is an interval of up to 170 p.c. of the normal before a stretch impulse appears; this interval is longer after 10 than 5 descending impulses but no greater for 20 or 50 than after 10; and the interval following this one is normal.

Thus after a number of descending impulses the interval following the last increases with the number of impulses up to about 10, and increases with the frequency of the descending impulses; the exact relationship of these quantities has not yet been fully worked out.

Theoretical treatment.

On the view set out above we imagine that after an impulse is set up the excitability of the receptor is lowered and returns to the level at which a further impulse is set up by the stimulus at a certain rate, the rate of this return of excitability itself determines the rate of response. It would appear that as the stimulus increases, the rate of return of excitability to this level also increases, for the response frequency becomes greater. This may be due to either or both of the following alternatives: (*a*) that the process of recovery of excitability is occurring more rapidly; (*b*) that the degree of recovery necessary for response decreases with increase of the stimulus.

A descending impulse early in recovery appears to be able either to lower the excitability of the ending more than other impulses of the series do, or else to delay the recovery process, it is impossible to determine which; but if activity in the ending is followed by an absolute refractory period, we should expect any impulse to lower the excitability to this rock-bottom level, and the prolonged interval might be attributed to slowed recovery. The similarity of Fig. 23 A and B suggests that the slowing produced continues throughout the whole recovery cycle, otherwise at the slower rate the delay caused by the descending impulses would not be the same fraction of the normal recovery time. When several descending impulses are set up at about the rate of the ending's own response, unless a descending impulse travelling over the polarized

surface of the ending leaves it in a state different from that left by an ascending impulse we should not expect there to be a prolonged interval after the last, for conditions of activity have not differed in any way from those of the ending's own response. If the impulses descend at a rate much greater than that of the ending's own response the interval after the last is prolonged, so that recovery to the response level is taking much longer than after any impulse of the ascending series. It is very surprising that the factors responsible for this do not make their presence felt beyond the first ascending impulse, but as the second appears after the normal interval they clearly do not, and the termination of the first prolonged interval by an impulse indicates that excitability has returned to a definite value—that at which response occurs to the stretch. Apparently after this the recovery rate is absolutely normal. It thus appears doubtful whether the slowing of recovery observed here can be ascribed to the same causes that lead to the progressive slowing of the response during activity ascribed to adaptation, which develops and disappears more slowly.

The transient lowering of excitability at the ending appears to be much the same whether caused by an ascending or descending impulse towards the end of the recovery period. In a previous paper [Matthews, 1931*b*] effects were described in frog's receptors, which suggested the hypothesis that descending impulses could reduce the adaptation of a nerve ending. In the present work no clear indication of this has been found, but in some preparations after rapid stimulation a consistent acceleration of 1–2 p.c. was found to follow the prolonged first interval after cessation of stimulation, and to last for several seconds; this acceleration is of the same order as the random irregularities that occur in the rhythm, but its consistent appearance in the preparations in which it was found suggests that it may be present here, but be far less marked than in the frog. As with the frog in many preparations no sign of it was to be found. In the cat's receptors the rhythm falls far more slowly with activity than it does in the frog, the smaller effect of descending impulses (when they have any effect) may be due to the same factors that lead to their slower adaptation. Clearly the matter does not merit further discussion until more experimental results are available.

It is interesting to compare the effects of antidromic impulses on the rhythmic response of the nerve ending with those produced on the rhythmic discharge of a motor neurone when impulses are backfired into it; these have been studied by Eccles and Hoff [1932]. The effects appear very similar; in both cases the rhythm is "reset," and after an

antidromic impulse the recovery of the rhythmic structure is delayed by an amount determined by the position of that impulse in the rhythmic cycle. Eccles and Hoff were not able to vary the rhythmic rate over a wide range, as is possible with the sensory ending, but in some of their experiments the behaviour with changed rate was identical with that found here, that the absolute value of the delay alters in proportion to the cyclic interval, while in others differences occurred with only slight alterations in the rhythmic rate.

From the sensory endings no sign has been found of the grouped discharges following the antidromic impulse which were frequently observed by these authors from the motor neurone.

The similarity of behaviour of the motor neurone and sensory ending suggests that much of their behaviour may result from the common properties of polarized surfaces; this has been suggested above for the nerve ending from other considerations.

Summary.

1. A method is described by which the impulses from single sensory nerve endings in mammalian muscle have been studied.

2. A new form of myograph assembly, which has been made for this work, is described.

3. Four distinct types of receptor have been identified. They are here designated A 1, A 2, B and C.

4. The rate of response of these receptors is roughly proportional to the logarithm of the tension on the muscle. Adaptation occurs very slowly.

5. Observations on the response to quick stretch and release suggest the end-organs containing A 1 and A 2 endings to have viscous elastic structure.

6. During active contraction the response of the A 1 receptors ceases; they behave as if they lie "in parallel" with the contractile elements.

7. During active contraction resulting from supramaximal stimulation the response of the A 2 endings accelerates, but if the stimulus is slightly submaximal it ceases. It is concluded that these endings lie in the muscle spindles and that only during supramaximal stimulation do the intrafusal fibres contract, and that when they do so they stimulate the A 2 nerve endings mechanically.

8. From the behaviour of the A 2 endings during twitch it is concluded that in soleus the intrafusal fibres are relatively more viscous than the ordinary muscle fibres.

9. The B endings have a high threshold and during contraction always behave as if they lie "in series" with the contractile elements. Their response depends only on the total tension on the muscle whether it be the result of passive stretch or active contraction.

10. The C endings lie in the fascia associated with muscles, they adapt rapidly, and only respond during movement of the muscle; they are few in number and probably not of great significance.

11. The time relations of impulses from A 1 receptors are slower than those from the A 2 and B receptors. They are thought to be travelling in smaller fibres.

12. Evidence is considered from which it is concluded that the A 1 response comes from the flower-spray endings of muscle spindles; the A 2 response from the annulo-spiral endings; the B response from the tendon organs of Ruffini.

13. The central effects of the impulses from these types of receptors are considered; it is thought that the A 1 response may be excitatory for the stretch reflex and the B response inhibitory. The function of the A 2 response cannot be decided from the present evidence.

14. When the circulation to the muscle is occluded, if the motor nerve be stimulated the excitability of the sensory nerve endings at first falls but later rises far above its normal level; finally in the absence of stretch a spontaneous discharge appears, its frequency rises to about 400 per sec. and after a minute or two it ceases and the ending is inexcitable until the circulation is released, when it rapidly recovers. This phenomenon is thought to be due to a breakdown of the nerve-ending mechanism. Theoretical aspects of this mechanism are considered.

15. The above effect is compared with the pain occurring in man when work is done by muscles with impeded circulation; the two have a number of common features. The possibility that the rapid discharge from stretch receptors may evoke pain is discussed.

16. The rhythmic mechanism of the end-organ is examined by observing the disturbance of rhythm brought about by antidromic impulses set up by electrical stimulation. The rhythm is "reset" by antidromic impulses which are followed by a delay the magnitude of which depends on the position of the antidromic impulse in the rhythmic cycle of the ending. Theoretical considerations are discussed and the behaviour of a nerve ending and motor neurone is compared; the effects produced by antidromic impulses are alike.

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